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# PASSMEDICINE NOTES

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# PASSMEDICINE NOTES CLINICAL SCIENCES

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# ANATOMY

## UPPER LIMB ANATOMY

The information below contains selected facts which commonly appear in examinations:

| Nerve | Motor | Sensory | Typical mechanism of injury & notes |
|---|---|---|---|
| Musculocutaneous nerve (C5-C7) | Elbow flexion (supplies biceps brachii) and supination | Lateral part of the forearm | Isolated injury rare - usually injured as part of brachial plexus injury |
| Axillary nerve (C5,C6) | Shoulder abduction (deltoid muscle) | Inferior region of the deltoid muscle | Humeral neck fracture/dislocation<br>Results in flattened deltoid |
| Radial nerve (C5-C8) | Extension (forearm, wrist, fingers, thumb) | Small area between the dorsal aspect of the 1st and 2nd metacarpals | Humeral midshaft fracture<br>Palsy results in wrist drop |
| Median nerve (C6, C8, T1) | LOAF* muscles<br>Features depend on the site of the lesion:<br>• wrist: paralysis of thenar muscles, opponens pollicis<br>• elbow: loss of pronation of forearm and weak wrist flexion | Palmar aspect of lateral 3½ fingers | Wrist lesion → carpal tunnel syndrome |
| Ulnar nerve (C8, T1) | Intrinsic hand muscles except LOAF*<br>Wrist flexion | Medial 1½ fingers | Medial epicondyle fracture<br>Damage may result in a 'claw hand' |
| Long thoracic nerve (C5-C7) | Serratus anterior | | Often during sport e.g. following a blow to the ribs. Also possible complication of mastectomy<br>Damage results in a winged scapula |

Erb-Duchenne palsy ('waiter's tip')

- due to damage of the upper trunk of the brachial plexus (C5,C6)
- may be secondary to shoulder dystocia during birth
- the arm hangs by the side and is internally rotated, elbow extended

Klumpke injury

- due to damage of the lower trunk of the brachial plexus (C8, T1)
- as above, may be secondary to shoulder dystocia during birth. Also may be caused by a sudden upward jerk of the hand
- associated with Horner's syndrome

*LOAF muscles

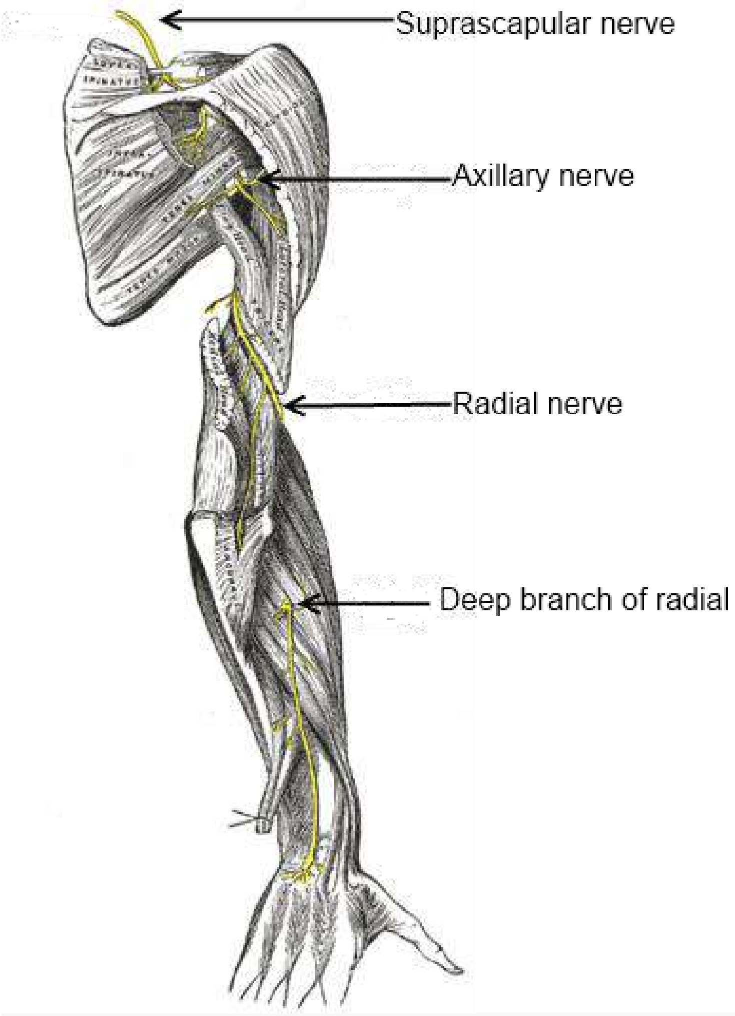
- Lateral two lumbricals
- Opponens pollis
- Abductor pollis brevis
- Flexor pollis brevis

# RADIAL NERVE

Continuation of posterior cord of the brachial plexus (root values C5 to T1)

Path

- In the axilla: lies posterior to the axillary artery on subscapularis, latissimus dorsi and teres major.
- Enters the arm between the brachial artery and the long head of triceps (medial to humerus).
- Spirals around the posterior surface of the humerus in the groove for the radial nerve.
- At the distal third of the lateral border of the humerus it then pierces the intermuscular septum and descends in front of the lateral epicondyle.
- At the lateral epicondyle it lies deeply between brachialis and brachioradialis where it then divides into a superficial and deep terminal branch.
- Deep branch crosses the supinator to become the posterior interosseous nerve.


Suprascapular nerve
Axillary nerve
Radial nerve
Deep branch of radial

In the image above the relationships of the radial nerve can be appreciated

## Regions innervated

| | |
|---|---|
| Motor (main nerve) | • Triceps<br>• Anconeus<br>• Brachioradialis<br>• Extensor carpi radialis |
| Motor (posterior interosseous branch) | • Supinator<br>• Extensor carpi ulnaris<br>• Extensor digitorum<br>• Extensor indicis<br>• Extensor digiti minimi<br>• Extensor pollicis longus and brevis<br>• Abductor pollicis longus |
| Sensory | The area of skin supplying the proximal phalanges on the dorsal aspect of the hand is supplied by the radial nerve (this does not apply to the little finger and part of the ring finger) |

## Muscular innervation and effect of denervation

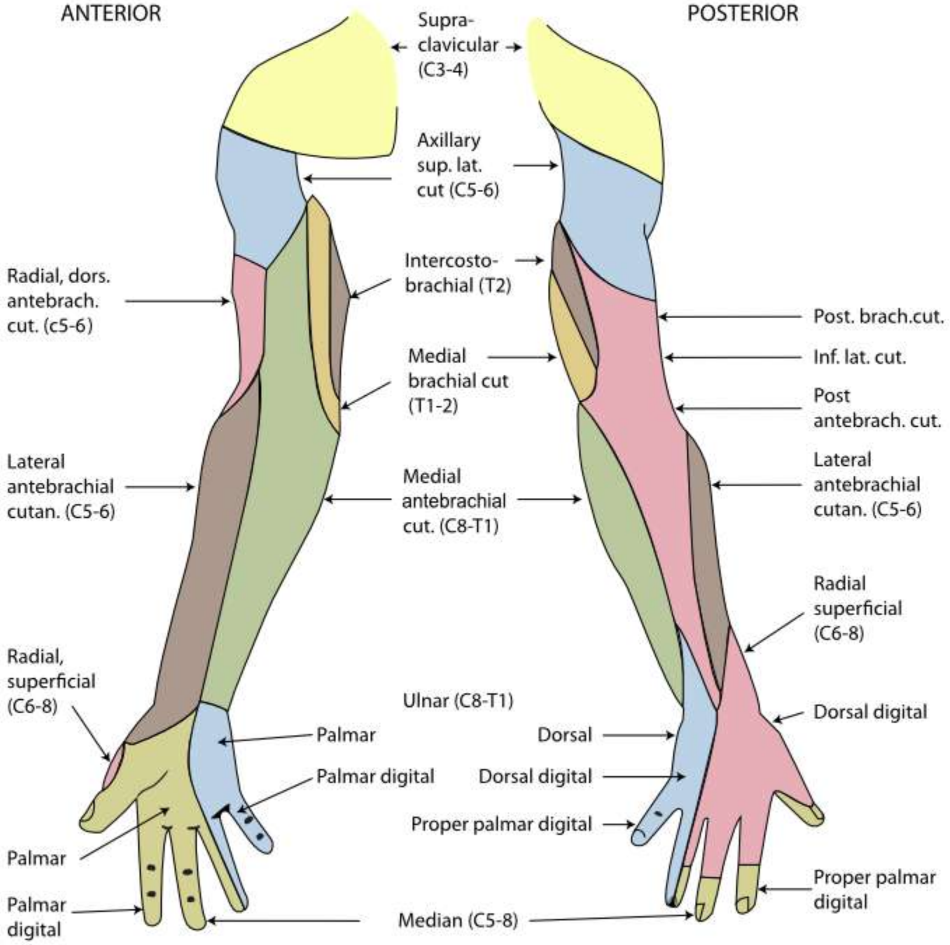
| Anatomical location | Muscle affected | Effect of paralysis |
|---|---|---|
| Shoulder | Long head of triceps | Minor effects on shoulder stability in abduction |
| Arm | Triceps | Loss of elbow extension |
| Forearm | Supinator<br>Brachioradialis<br>Extensor carpi radialis longus and brevis | Weakening of supination of prone hand and elbow flexion in mid prone position |

Patterns of damage

- wrist drop
- sensory loss to small area between the dorsal aspect of the 1st and 2nd metacarpals

Axillary damage

- as above
- paralysis of triceps


ANTERIOR
POSTERIOR
Supra-clavicular (C3-4)
Axillary sup. lat. cut (C5-6)
Radial, dors. antebrach. cut. (c5-6)
Intercosto-brachial (T2)
Post. brach.cut.
Inf. lat. cut.
Medial brachial cut (T1-2)
Post antebrach. cut.
Lateral antebrachial cutan. (C5-6)
Medial antebrachial cut. (C8-T1)
Lateral antebrachial cutan. (C5-6)
Radial superficial (C6-8)
Radial, superficial (C6-8)
Ulnar (C8-T1)
Dorsal digital
Palmar
Dorsal
Palmar digital
Dorsal digital
Proper palmar digital
Palmar
Proper palmar digital
Palmar digital
Median (C5-8)

The cutaneous sensation of the upper limb- illustrating the contribution of the radial nerve

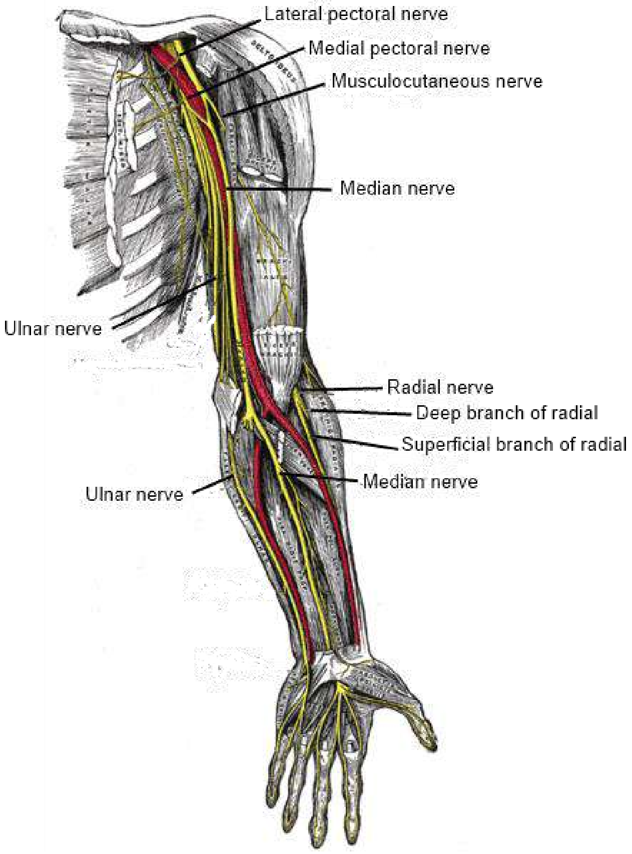
# ULNAR NERVE

Overview
- arises from medial cord of brachial plexus (C8, T1)

Motor to
- medial two lumbricals
- aDductor pollicis
- interossei
- hypothenar muscles: abductor digiti minimi, flexor digiti minimi
- flexor carpi ulnaris

Sensory to
- medial 1 1/2 fingers (palmar and dorsal aspects)

Path
- the ulnar nerve travels through the posteromedial aspect of the upper arm to the flexor compartment of the forearm
- it then enters the palm of the hand via the Guyon's canal, superficial to the flexor retinaculum and lateral to the pisiform bone


Lateral pectoral nerve
Medial pectoral nerve
Musculocutaneous nerve
Median nerve
Ulnar nerve
Radial nerve
Deep branch of radial
Superficial branch of radial
Ulnar nerve
Median nerve

**Branches**

| Branch | Supplies |
|---|---|
| Muscular branch | Flexor carpi ulnaris<br>Medial half of the flexor digitorum profundus |
| Palmar cutaneous branch (Arises near the middle of the forearm) | Skin on the medial part of the palm |
| Dorsal cutaneous branch | Dorsal surface of the medial part of the hand |
| Superficial branch | Cutaneous fibres to the anterior surfaces of the medial one and one-half digits |
| Deep branch | Hypothenar muscles<br>All the interosseous muscles<br>Third and fourth lumbricals<br>Adductor pollicis<br>Medial head of the flexor pollicis brevis |

**Patterns of damage**

Damage at wrist

- 'claw hand' - hyperextension of the metacarpophalangeal joints and flexion at the distal and proximal interphalangeal joints of the 4th and 5th digits
- wasting and paralysis of intrinsic hand muscles (except lateral two lumbricals)
- wasting and paralysis of hypothenar muscles
- sensory loss to the medial 1 1/2 fingers (palmar and dorsal aspects)

Damage at elbow

- as above (however, ulnar paradox - clawing is more severe in distal lesions)
- radial deviation of wrist

# LOWER LIMB ANATOMY

The information below contains selected facts which commonly appear in examinations:

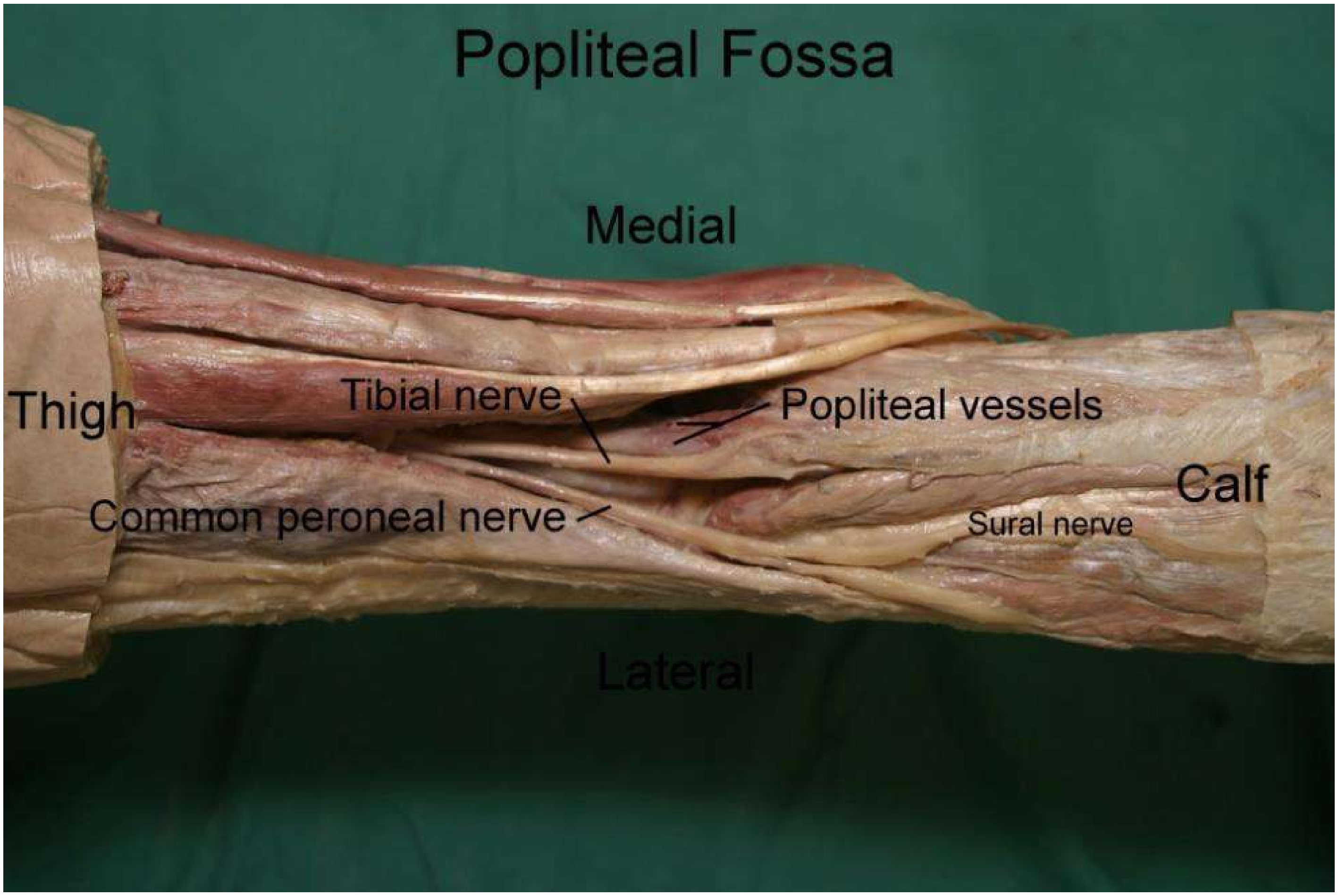
| Nerve | Motor | Sensory | Typical mechanism of injury & notes |
|---|---|---|---|
| Femoral nerve | Knee extension, thigh flexion | Anterior and medial aspect of the thigh and lower leg | Hip and pelvic fractures<br>Stab/gunshot wounds |
| Obturator nerve | Thigh adduction | Medial thigh | Anterior hip dislocation |
| Lateral cutaneous nerve of the thigh | None | Lateral and posterior surfaces of the thigh | Compression of the nerve near the ASIS → meralgia paraesthetica, a condition characterised by pain, tingling and numbness in the distribution of the lateral cutaneous nerve |
| Tibial nerve | Foot plantarflexion and inversion | Sole of foot | Not commonly injured as deep and well protected.<br>Popliteral lacerations, posterior knee dislocation |
| Common peroneal nerve | Foot dorsiflexion and eversion<br>Extensor hallucis longus | Dorsum of the foot and the lower lateral part of the leg | Injury often occurs at the neck of the fibula<br>Tightly applied lower limb plaster cast<br><br>Injury causes foot drop |
| Superior gluteal nerve | Hip abduction | None | Misplaced intramuscular injection<br>Hip surgery<br>Pelvic fracture<br>Posterior hip dislocation<br><br>**Injury results in a positive Trendelenburg sign** |
| Inferior gluteal nerve | Hip extension and lateral rotation | None | Generally injured in association with the sciatic nerve<br><br>Injury results in difficulty rising from seated position.<br>Can't jump, can't climb stairs |

# POPLITEAL FOSSA

### Boundaries of the popliteal fossa

| | |
|---|---|
| **Laterally** | Biceps femoris above, lateral head of gastrocnemius and plantaris below |
| **Medially** | Semimembranosus and semitendinosus above, medial head of gastrocnemius below |
| **Floor** | Popliteal surface of the femur, posterior ligament of knee joint and popliteus muscle |
| **Roof** | Superficial and deep fascia |

### Image showing the popliteal fossa


Popliteal Fossa
Medial
Thigh
Tibial nerve
Popliteal vessels
Calf
Common peroneal nerve
Sural nerve
Lateral

**Contents**

- Popliteal artery and vein
- Small saphenous vein
- Common peroneal nerve
- Tibial nerve
- Posterior cutaneous nerve of the thigh
- Genicular branch of the obturator nerve
- Lymph nodes

## EPIDERMIS

The epidermis is the outermost layer of the skin and is composed of a stratified squamous epithelium with an underlying basal lamina

It may be divided in to five layers:

| Layer | Description |
|---|---|
| Stratum corneum | Flat, dead, scale-like cells filled with keratin<br>Continually shed |
| Stratum lucidum | Clear layer - present in thick skin only |

| Layer | Description |
|---|---|
| Stratum granulosum | Cells form links with neighbours |
| Stratum spinosum | Squamous cells begin keratin synthesis<br>Thickest layer of epidermis |
| Stratum germinativum | The basement membrane - single layer of columnar epithelial cells<br>Gives rise to keratinocytes<br>Contains melanocytes |

# RENAL ANATOMY

Each kidney is about 11cm long, 5cm wide and 3cm thick. They are located in a deep gutter alongside the projecting vertebral bodies, on the anterior surface of psoas major. In most cases the left kidney lies approximately 1.5cm higher than the right. The upper pole of both kidneys approximates with the 11th rib (beware pneumothorax during nephrectomy). On the left hand side the hilum is located at the L1 vertebral level and the right kidney at level L1-2. The lower border of the kidneys is usually alongside L3.

## Relations

The tables below show the anatomical relations of the kidneys:

| Relations | Right Kidney | Left Kidney |
|---|---|---|
| Posterior | Quadratus lumborum, diaphragm, psoas major, transversus abdominis | Quadratus lumborum, diaphragm, psoas major, transversus abdominis |
| Anterior | Hepatic flexure of colon | Stomach, Pancreatic tail |
| Superior | Liver, adrenal gland | Spleen, adrenal gland |

If we consider relations according to whether they are in direct contact or whether there is peritoneum in-between:

Right kidney

| Direct contact | Layer of peritoneum in-between |
|---|---|
| Right suprarenal gland<br>Duodenum<br>Colon | Liver<br>Distal part of small intestine |

Left kidney

| Direct contact | Layer of peritoneum in-between |
|---|---|
| Left suprarenal gland<br>Pancreas<br>Colon | Stomach<br>Spleen<br>Distal part of small intestine |

## Fascial covering

Each kidney and suprarenal gland is enclosed within a common layer of investing fascia, derived from the transversalis fascia. It is divided into anterior and posterior layers (Gerotas fascia).

## Renal structure

Kidneys are surrounded by an outer cortex and an inner medulla which usually contains between 6 and 10 pyramidal structures. The papilla marks the innermost apex of these. They terminate at the renal pelvis, into the ureter.

Lying in a hollow within the kidney is the renal sinus. This contains:
1. Branches of the renal artery
2. Tributaries of the renal vein
3. Major and minor calyces's
4. Fat

**Structures at the renal hilum**
The renal vein lies most anteriorly, then renal artery (it is an end artery) and the ureter lies most posterior.

# FORAMINA OF THE SKULL

Questions asking about foramina of the skull have come up in the exam in previous years. Below is a brief summary of the major foramina, please see the Wikipedia link for a full list.

| Foramen | Bone | Vessels | Nerves |
|---|---|---|---|
| Optic canal | Sphenoid | Ophthalmic artery | Optic nerve (II) |
| Superior orbital fissure | Sphenoid | Superior ophthalmic vein<br>Inferior ophthalmic vein | Oculomotor nerve (III)<br>Trochlear nerve (IV)<br>lacrimal, frontal and nasociliary branches of ophthalmic nerve (V1)<br>Abducent nerve (VI) |
| Inferior orbital fissure | Sphenoid and maxilla | Inferior ophthalmic veins<br>Infraorbital artery<br>Infraorbital vein | Zygomatic nerve and infraorbital nerve of maxillary nerve (V2)<br>Orbital branches of pterygopalatine ganglion |
| Foramen rotundum | Sphenoid | - | Maxillary nerve (V2) |
| Foramen ovale | Sphenoid | Accessory meningeal artery | Mandibular nerve (V3) |
| Jugular foramen | Occipital and temporal | Posterior meningeal artery<br>Ascending pharyngeal artery<br>Inferior petrosal sinus<br>Sigmoid sinus<br>Internal jugular vein | Glossopharyngeal nerve (IX)<br>Vagus nerve (X)<br>Accessory nerve (XI) |

# CRANIAL NERVES

The table below lists the major characteristics of the 12 cranial nerves:

| Nerve | Functions | Clinical | Pathway/foramen |
|---|---|---|---|
| I (Olfactory) | Smell | | Cribriform plate |
| II (Optic) | Sight | | Optic canal |
| III (Oculomotor) | Eye movement (MR, IO, SR, IR)<br>Pupil constriction<br>Accomodation<br>Eyelid opening | Palsy results in<br>• ptosis<br>• 'down and out' eye<br>• dilated, fixed pupil | Superior orbital fissure (SOF) |
| IV (Trochlear) | Eye movement (SO) | Palsy results in defective downward gaze → vertical diplopia | SOF |
| V (Trigeminal) | Facial sensation<br>Mastication | Lesions may cause:<br>• trigeminal neuralgia<br>• loss of corneal reflex (afferent)<br>• loss of facial sensation<br>• paralysis of mastication muscles<br>• deviation of jaw to weak side | $V_1$: SOF, $V_2$: Foramen rotundum,<br>$V_3$: Foramen ovale |
| VI (Abducens) | Eye movement (LR) | Palsy results in defective abduction → horizontal diplopia | SOF |
| VII (Facial) | Facial movement<br>Taste (anterior 2/3rds of tongue)<br>Lacrimation<br>Salivation | Lesions may result in:<br>• flaccid paralysis of upper + lower face<br>• loss of corneal reflex (efferent)<br>• loss of taste<br>• hyperacusis | Internal auditory meatus |
| VIII (Vestibulocochlear) | Hearing, balance | Hearing loss<br>Vertigo, nystagmus<br>Acoustic neuromas are Schwann cell tumours of the cochlear nerve | Internal auditory meatus |
| IX (Glossopharyngeal) | Taste (posterior 1/3rd of tongue) | Lesions may result in; | Jugular foramen |

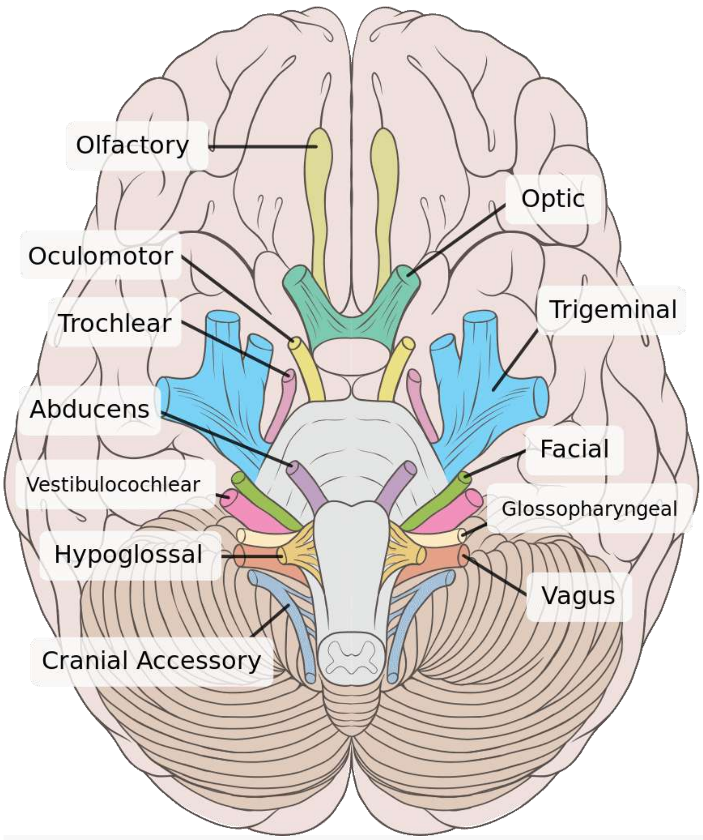
| Nerve | Functions | Clinical | Pathway/foramen |
|---|---|---|---|
|  | Salivation<br>Swallowing<br>Mediates input from carotid body & sinus | • hypersensitive carotid sinus reflex<br>• loss of gag reflex (afferent) |  |
| X (Vagus) | Phonation<br>Swallowing<br>Innervates viscera | Lesions may result in;<br>• uvula deviates away from site of lesion<br>• loss of gag reflex (efferent) | Jugular foramen |
| XI (Accessory) | Head and shoulder movement | Lesions may result in;<br>• weakness turning head to contralateral side | Jugular foramen |
| XII (Hypoglossal) | Tongue movement | Tongue deviates towards side of lesion | Hypoglossal canal |

Some cranial nerves are motor, some sensory and some are both. The most useful mnemonic is given below.

CN I -------------------------------------------------------------------→XII

**S**ome **S**ay **M**arry **M**oney **B**ut **M**y **B**rother **S**ays **B**ig **B**rains **M**atter **M**ost

**S** = Sensory, **M** = Motor, **B** = Both


Olfactory
Optic
Oculomotor
Trochlear
Trigeminal
Abducens
Facial
Vestibulocochlear
Glossopharyngeal
Hypoglossal
Vagus
Cranial Accessory

View from the inferior surface of the brain showing the emergence of the cranial nerves

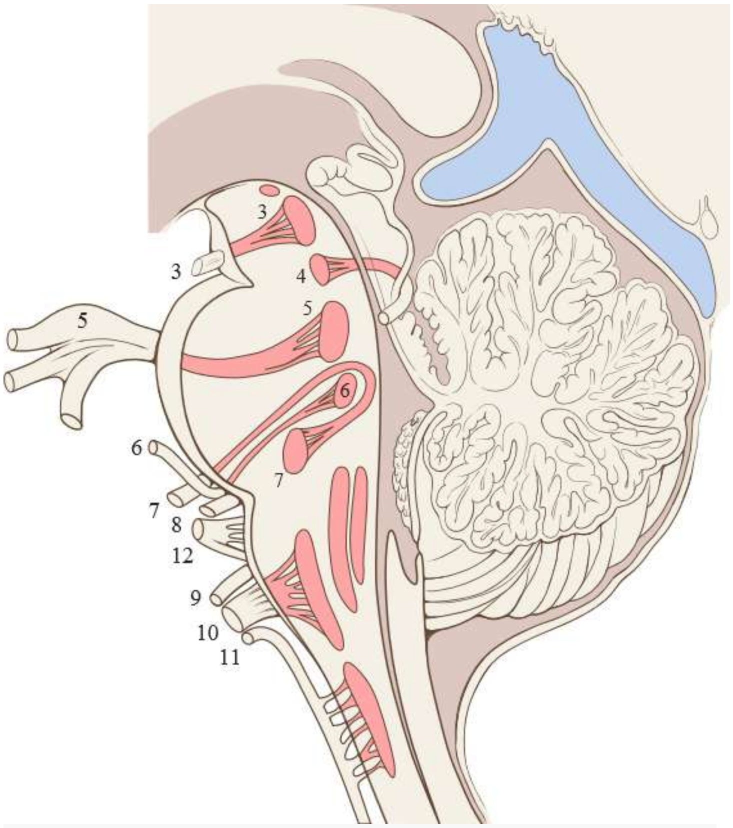

3
3
4
5
5
6
6
7
7
8
12
9
10
11

Diagram showing the nuclei of the cranial nerves in the brainstem

## Cranial nerve reflexes

| Reflex | Afferent limb | Efferent limb |
|---|---|---|
| Corneal | Ophthalmic nerve ($V_1$) | Facial nerve (VII) |
| Jaw jerk | Mandibular nerve ($V_3$) | Mandibular nerve ($V_3$) |
| Gag | Glossopharyngeal nerve (IX) | Vagal nerve (X) |
| Carotid sinus | Glossopharyngeal nerve (IX) | Vagal nerve (X) |
| Pupillary light | Optic nerve (II) | Oculomotor nerve (III) |
| Lacrimation | Ophthalmic nerve ($V_1$) | Facial nerve (VII) |

# SPINAL CORD

- Located in a canal within the vertebral column that affords it structural support.

- Rostrally it continues to the medulla oblongata of the brain and caudally it tapers at a level corresponding to the L1-2 interspace (in the adult), a central structure, the filum terminale anchors the cord to the first coccygeal vertebra.
- The spinal cord is characterised by cervico-lumbar enlargements and these, broadly speaking, are the sites which correspond to the brachial and lumbar plexuses respectively.

There are some key points to note when considering the surgical anatomy of the spinal cord:

* During foetal growth the spinal cord becomes shorter than the spinal canal, hence the adult site of cord termination at the **L1-2** level.

* Due to growth of the vertebral column the spine segmental levels may not always correspond to bony landmarks as they do in the cervical spine.

* The spinal cord is incompletely divided into two symmetrical halves by a **dorsal median sulcus** and **ventral median fissure**. Grey matter surrounds a central canal that is continuous rostrally with the ventricular system of the CNS.

* The grey matter is sub divided cytoarchitecturally into **Rexeds laminae**.

* Afferent fibres entering through the dorsal roots usually terminate near their point of entry but may travel for varying distances in **Lissauers tract**. In this way they may establish synaptic connections over several levels

* At the tip of the dorsal horn are afferents associated with nociceptive stimuli. The ventral horn contains neurones that innervate skeletal muscle.

The key point to remember when revising CNS anatomy is to keep a clinical perspective in mind. So it is worth classifying the ways in which the spinal cord may become injured. These include:

**Trauma** either direct or as a result of disc protrusion
**Neoplasia** either by direct invasion (rare) or as a result of pathological vertebral fracture
**Inflammatory diseases** such as Rheumatoid disease, or OA (formation of osteophytes compressing nerve roots etc.
**Vascular** either as a result of stroke (rare in cord) or as complication of aortic dissection
**Infection** historically diseases such as TB, epidural abscesses.

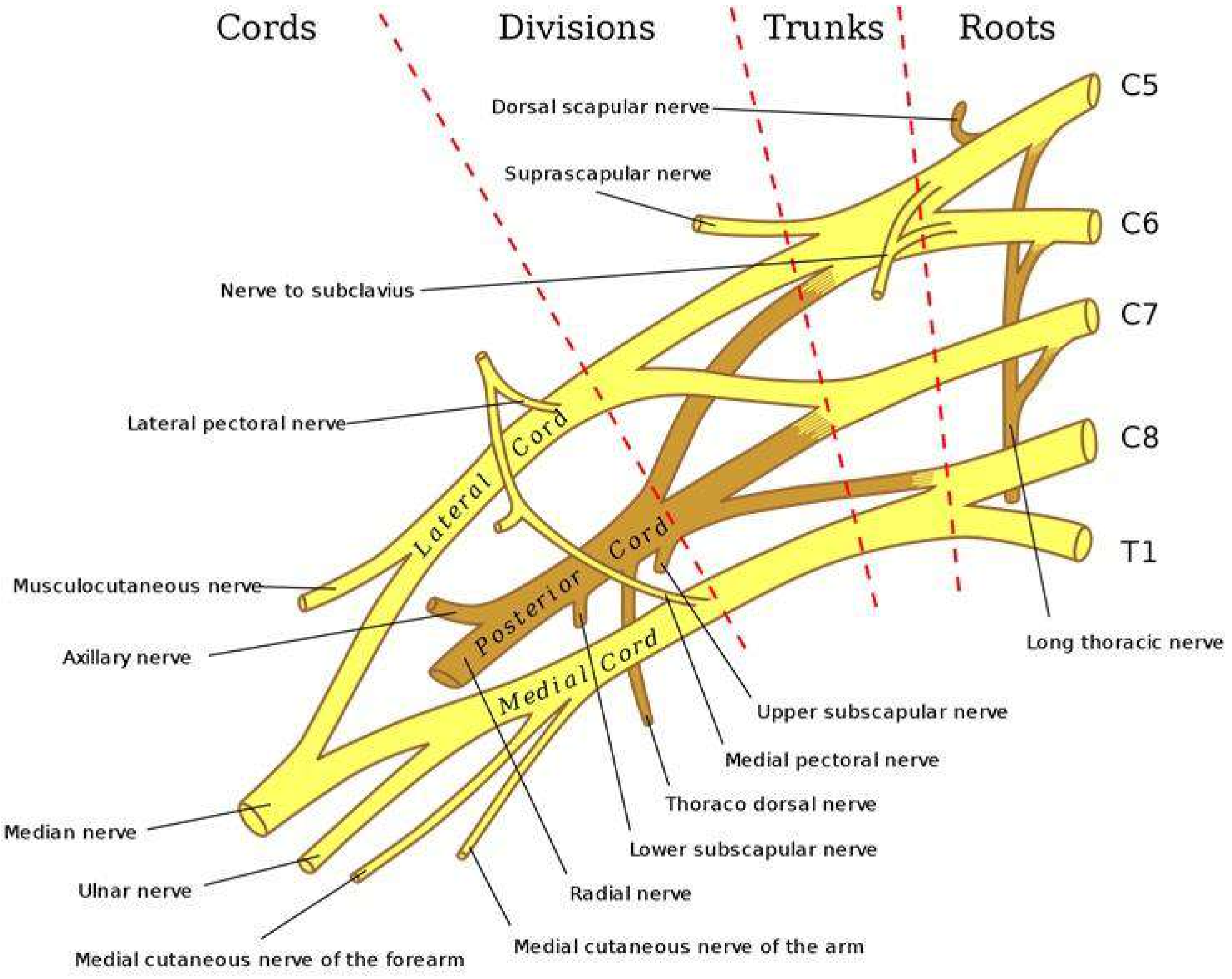
The anatomy of the cord will, to an extent dictate the clinical presentation. Some points/ conditions to remember:

- Brown- Sequard syndrome-Hemisection of the cord producing ipsilateral loss of proprioception and upper motor neurone signs, plus contralateral loss of pain and temperature sensation. The explanation of this is that the fibres decussate at different levels.
- Lesions below L1 will tend to present with lower motor neurone signs

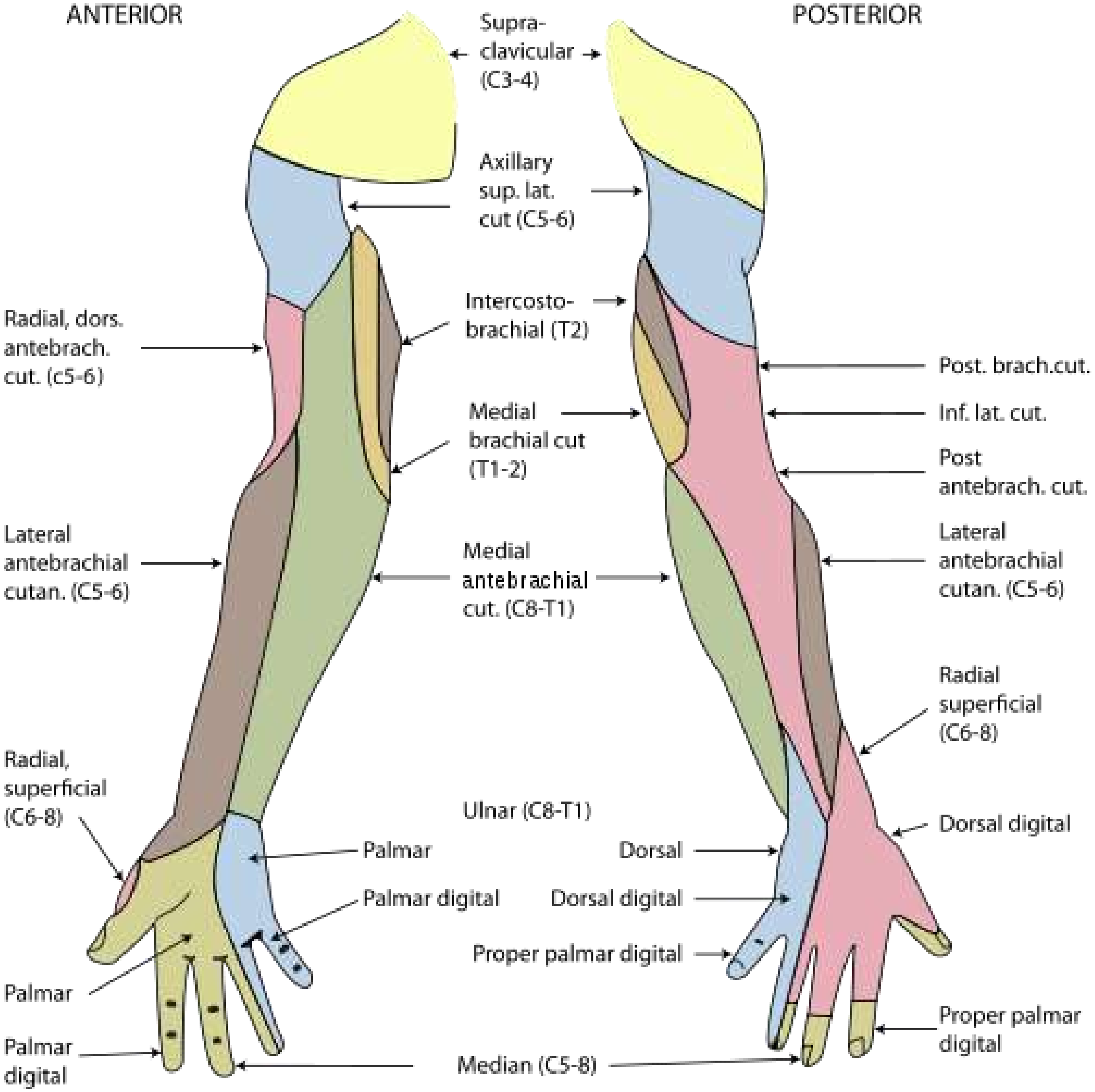
# BRACHIAL PLEXUS

| | |
|---|---|
| **Origin** | Anterior rami of C5 to T1 |
| **Sections of the plexus** | - Roots, trunks, divisions, cords, branches<br>- Mnemonic:*Real Teenagers Drink Cold Beer* |
| **Roots** | - Located in the posterior triangle<br>- Pass between scalenus anterior and medius |
| **Trunks** | - Located posterior to middle third of clavicle<br>- Upper and middle trunks related superiorly to the subclavian artery<br>- Lower trunk passes over 1st rib posterior to the subclavian artery |
| **Divisions** | Apex of axilla |
| **Cords** | Related to axillary artery |

*Diagram illustrating the branches of the brachial plexus*


Cords
Divisions
Trunks
Roots
C5
C6
C7
C8
T1
Dorsal scapular nerve
Suprascapular nerve
Nerve to subclavius
Lateral pectoral nerve
Lateral Cord
Musculocutaneous nerve
Axillary nerve
Posterior Cord
Medial Cord
Long thoracic nerve
Upper subscapular nerve
Medial pectoral nerve
Thoraco dorsal nerve
Lower subscapular nerve
Radial nerve
Median nerve
Ulnar nerve
Medial cutaneous nerve of the forearm
Medial cutaneous nerve of the arm

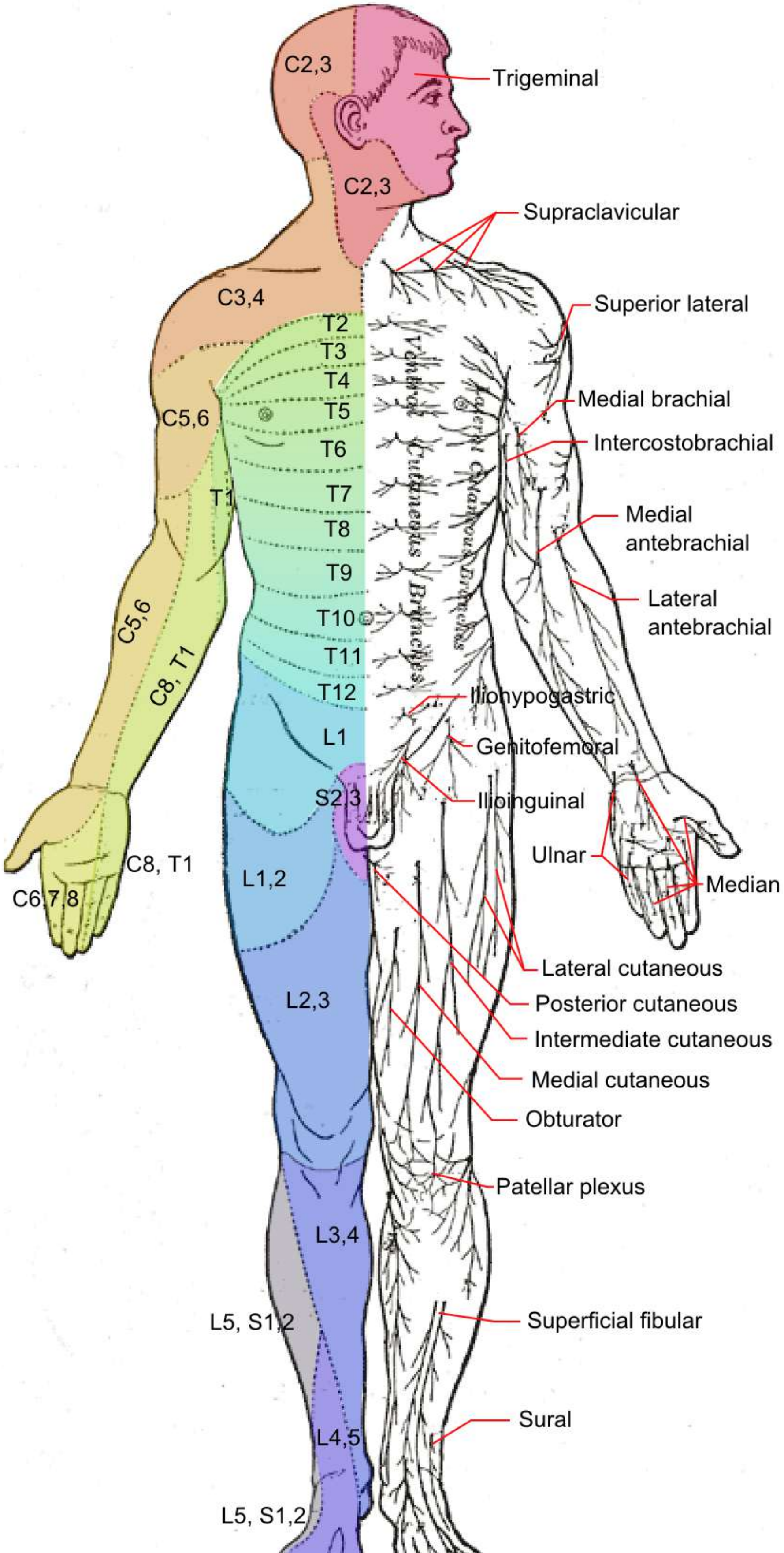
## Cutaneous sensation of the upper limb

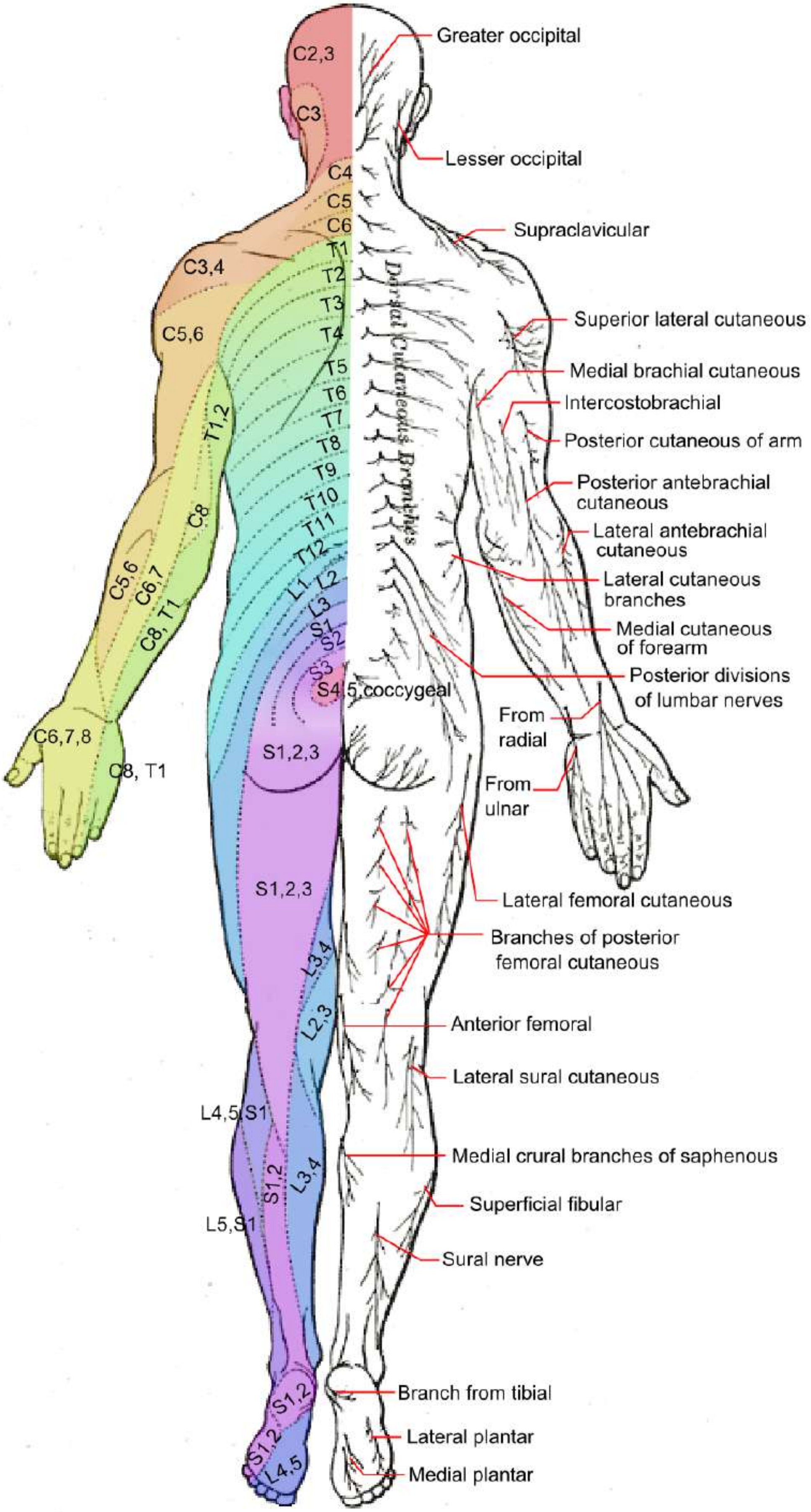

ANTERIOR
POSTERIOR
Supra-clavicular (C3-4)
Axillary sup. lat. cut (C5-6)
Radial, dors. antebrach. cut. (c5-6)
Intercosto-brachial (T2)
Post. brach.cut.
Medial brachial cut (T1-2)
Inf. lat. cut.
Post antebrach. cut.
Lateral antebrachial cutan. (C5-6)
Medial antebrachial cut. (C8-T1)
Lateral antebrachial cutan. (C5-6)
Radial superficial (C6-8)
Radial, superficial (C6-8)
Ulnar (C8-T1)
Dorsal digital
Palmar
Dorsal
Palmar digital
Dorsal digital
Proper palmar digital
Palmar
Proper palmar digital
Palmar digital
Median (C5-8)

# DERMATOMES

The table below lists the major dermatome landmarks:

| Nerve root | Landmark | Mnemonics |
|---|---|---|
| C2 | Posterior half of the skull (cap) | |
| C3 | High turtleneck shirt | |
| C4 | Low-collar shirt | |
| C5 | Ventral axial line of upper limb | |
| C6 | Thumb + index finger | Make a 6 with your left hand by touching the tip of the thumb & index finger together - C6 |
| C7 | Middle finger + palm of hand | |
| C8 | Ring + little finger | |
| T4 | Nipples | T4 at the Teat Pore |
| T5 | Inframammary fold | |
| T6 | Xiphoid process | |
| T10 | Umbilicus | BellybuT-TEN |
| L1 | Inguinal ligament | L for ligament, 1 for 1nguinal |
| L4 | Knee caps | Down on aLL fours - L4 |
| L5 | Big toe, dorsum of foot (except lateral aspect) | L5 = Largest of the 5 toes |
| S1 | Lateral foot, small toe | S1 = the smallest one |
| S2, S3 | Genitalia | |


C2,3
Trigeminal
C2,3
Supraclavicular
C3,4
Superior lateral
T2
T3
T4
T5
C5,6
Medial brachial
Intercostobrachial
T6
T1
T7
T8
Medial antebrachial
T9
Lateral antebrachial
C5,6
T10
C8, T1
T11
T12
Iliohypogastric
L1
Genitofemoral
S2,3
Ilioinguinal
Ulnar
C8, T1
L1,2
Median
C6,7,8
Lateral cutaneous
Posterior cutaneous
L2,3
Intermediate cutaneous
Medial cutaneous
Obturator
Patellar plexus
L3,4
L5, S1,2
Superficial fibular
Sural
L4,5
L5, S1,2
Ventral Cutaneous Branches
Lateral Cutaneous Branches


C2,3
C3
C4
C5
C6
T1
C3,4
T2
T3
C5,6
T4
T5
T6
T1,2
T7
T8
T9
T10
C8
T11
T12
C5,6
C6,7
L1
L2
L3
C8, T1
S1
S2
S3
S4,5,coccygeal
C6,7,8
S1,2,3
C8, T1
S1,2,3
L3,4
L2,3
L4,5,S1
S1,2
L3,4
L5,S1
S1,2
S1,2
L4,5
Dorsal Cutaneous Branches
Greater occipital
Lesser occipital
Supraclavicular
Superior lateral cutaneous
Medial brachial cutaneous
Intercostobrachial
Posterior cutaneous of arm
Posterior antebrachial cutaneous
Lateral antebrachial cutaneous
Lateral cutaneous branches
Medial cutaneous of forearm
Posterior divisions of lumbar nerves
From radial
From ulnar
Lateral femoral cutaneous
Branches of posterior femoral cutaneous
Anterior femoral
Lateral sural cutaneous
Medial crural branches of saphenous
Superficial fibular
Sural nerve
Branch from tibial
Lateral plantar
Medial plantar

# COLLAGEN

Collagen is the main structural protein found in connective tissue and is the most common protein found in the body.

Whilst over 20 types of collagen have been identified there are 4-5 which are considered the most important:

| Collagen type | Notes | Associated conditions |
|---|---|---|
| I | Bone, skin, tendon | Osteogenesis imperfecta |
| II | Hyaline cartilage, vitreous humour | |
| III | Reticular fibre, granulation tissue | Vascular variant of Ehlers-Danlos syndrome |
| IV | Basal lamina, lens, basement membrane | Alport syndrome, Goodpasture's syndrome |
| V | Most interstitial tissue, placental tissue | Classical variant of Ehlers-Danlos syndrome |

Structure

- Composed of 3 polypeptide strands that are woven into a helix, usually a combination of glycine with either proline or hydroxyproline plus another amino acid
- Numerous hydrogen bonds exist within molecule to provide additional strength
- Many subtypes but commonest subtype is I (90% of bodily collagen), tissues with increased levels of flexibility have increased levels of type III collagen
- Vitamin C is important in establishing cross-links
- Synthesised by fibroblasts

**Collagen diseases**

Disorders of collagen range from relatively common, acquired defects (typically aging), through to rarer congenital disorders. The latter are exemplified by conditions such as osteogenesis imperfecta and Ehlers Danlos syndromes.

Osteogenesis imperfecta:

- 8 Subtypes
- Defect of type I collagen
- In type I the collagen is normal quality but insufficient quantity
- Type II- poor quantity and quality
- Type III- Collagen poorly formed, normal quantity
- Type IV- Sufficient quantity but poor quality
- Patients have bones which fracture easily, loose joint and multiple other defects depending upon which sub type they suffer from.

Ehlers Danlos:

- Multiple sub types
- Abnormality of types 1 and 3 collagen
- Patients have features of hypermobility.

- Individuals are prone to joint dislocations and pelvic organ prolapse. In addition to many other diseases related to connective tissue defects.

# PHYSIOLOGY AND BIOCHEMISTRY

## CELL ORGANELLES

The table below summarises the main functions of the major cell organelles:

| Organelle/macromolecule | Main function |
|---|---|
| Endoplasmic reticulum | Rough endoplasmic reticulum<br>• translation and folding of new proteins<br>• manufacture of lysosomal enzymes<br>• site of N-linked glycosylation<br>• examples of cells with extensive RER include pancreatic cells, goblet cells, plasma cells<br>Smooth endoplasmic reticulum<br>• steroid, lipid synthesis<br>• examples of cells with extensive SER include those of the adrenal cortex, hepatocytes, testes, ovaries |
| Golgi apparatus | Modifies, sorts, and packages these molecules that are destined for cell secretion<br>Site of O-linked glycosylation |
| Mitochondrion | Aerobic respiration. Contains mitochondrial genome as circular DNA |
| Nucleus | DNA maintenance and RNA transcription |
| Lysosome | Breakdown of large molecules such as proteins and polysaccharides |
| Nucleolus | Ribosome production |
| Ribosome | Translation of RNA into proteins |
| Peroxisome | Catabolism of very long chain fatty acids and amino acids<br>Results in the formation of hydrogen peroxide |
| Proteasome | Along with the lysosome pathway involved in degradation of protein molecules that have been tagged with ubiquitin |

## CELL CYCLE

The cell cycle is regulated by proteins called cyclins which in turn control cyclin-dependent kinase (CDK) enzymes.

| Phase | Notes | Regulatory proteins |
|---|---|---|
| $G_0$ | - 'resting' phase<br>- quiescent cells such as hepatocytes and more permanently resting cells such as neurons | |
| $G_1$ | - **G**ap 1, cells increase in size<br>- determines length of cell cycle<br>- under influence of p53 | Cyclin D / CDK4, Cyclin D / CDK6 and Cyclin E / CDK2: regulates transition from G1 to S phase |
| S | - **S**ynthesis of DNA, RNA and histone<br>- centrosome duplication | Cyclin A / CDK2: active in S phase |
| $G_2$ | - **G**ap 2, cells continue to increase in size | Cyclin B / CDK1: regulates transition from $G_2$ to M phase |
| M | - **M**itosis - cell division<br>- the shortest phase of the cell cycle | |

# CELL DIVISION

There are two types of cell division; mitosis and meiosis.

The table below demonstrates the key differences:

| Mitosis | Meiosis |
|---|---|
| Occurs in somatic cells | Occurs in gametes |
| Results in 2 diploid daughter cells | Results in 4 haploid daughter cells |
| Daughter cells are genetically identical to parent cell | Daughter cells contain one homologue of each chromosome pair and are therefore genetically different |

Remember:

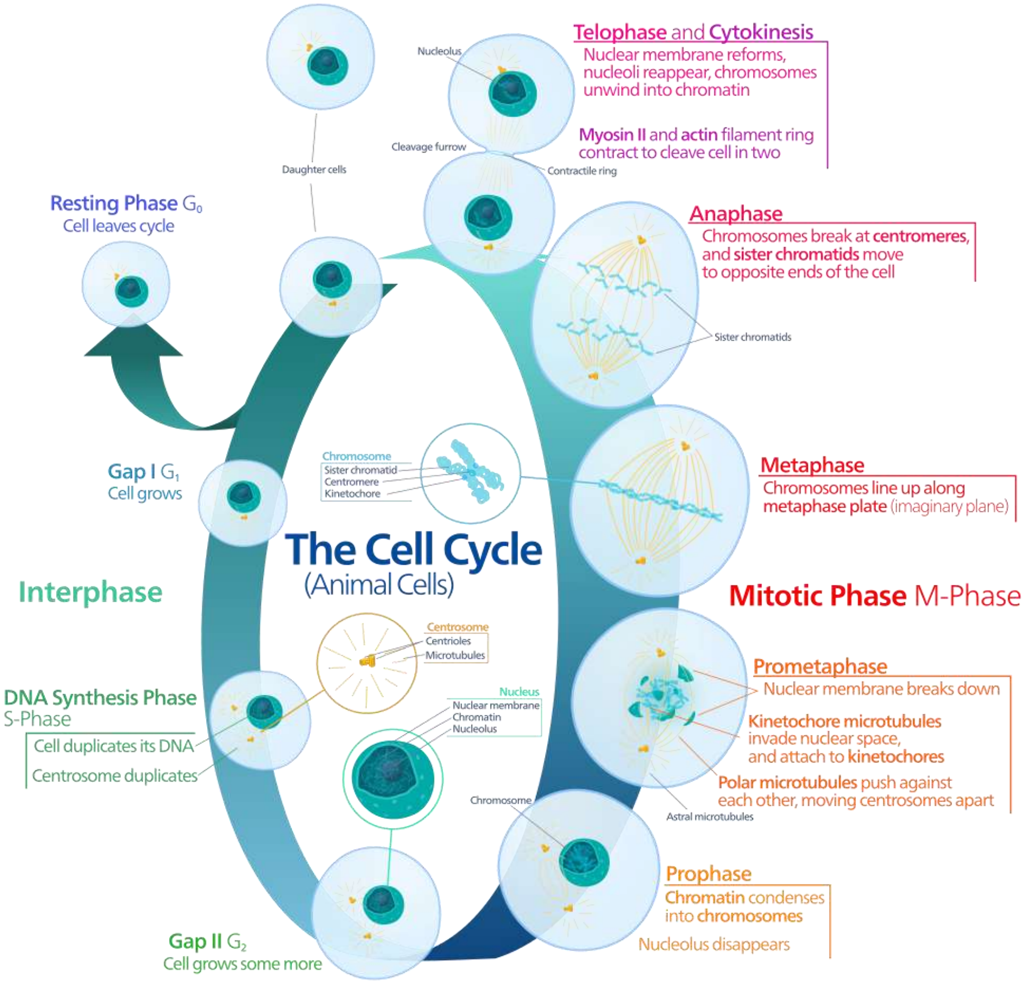
- somatic cells have 22 pairs of autosomes and 1 pair of sex chromosomes, i.e. 46XY or 46XX
- cells with a normal chromosome complement are known as diploid cells
- gametes (ova or spermatozoa) have a single copy of each chromosome and are known as haploid cells

### Mitosis

Mitosis occurs during the M phase of the cell cycle. It describes the process in which somatic cells divide and replicate producing genetically identical diploid daughter cells. This allows tissue to grow and renew itself.

During the S phase of the cell cycle the cell prepares itself for division by duplicating the chromosomes. The table below shows the phases of mitosis itself:

| Prophase | Chromatin in the nucleus condenses |
|---|---|
| **Prometaphase** | Nuclear membrane breaks down allowing the microtubules to attach to the chromosomes |
| **Metaphase** | Chromosomes aligned at middle of cell |
| **Anaphase** | The paired chromosomes separate at the kinetochores and move to opposite sides of the cell |
| **Telophase** | Chromatids arrive at opposite poles of cell |
| **Cytokinesis** | Actin-myosin complex in the centre of the cell contacts resulting in it being 'pinched' into two daughter cells |


Telophase and Cytokinesis
Nuclear membrane reforms, nucleoli reappear, chromosomes unwind into chromatin
Myosin II and actin filament ring contract to cleave cell in two
Nucleolus
Cleavage furrow
Contractile ring
Daughter cells
Resting Phase $G_0$
Cell leaves cycle
Anaphase
Chromosomes break at centromeres, and sister chromatids move to opposite ends of the cell
Sister chromatids
Gap I $G_1$
Cell grows
Chromosome
Sister chromatid
Centromere
Kinetochore
The Cell Cycle
(Animal Cells)
Metaphase
Chromosomes line up along metaphase plate (imaginary plane)
Mitotic Phase M-Phase
Interphase
Centrosome
Centrioles
Microtubules
Nucleus
Nuclear membrane
Chromatin
Nucleolus
DNA Synthesis Phase
S-Phase
Cell duplicates its DNA
Centrosome duplicates
Prometaphase
Nuclear membrane breaks down
Kinetochore microtubules invade nuclear space, and attach to kinetochores
Polar microtubules push against each other, moving centrosomes apart
Astral microtubules
Chromosome
Prophase
Chromatin condenses into chromosomes
Nucleolus disappears
Gap II $G_2$
Cell grows some more

## MICROTUBULES

Microtubules are components of the cytoskeleton of the cytoplasm. They help guide movement during intracellular transport and also help bind internal organelles. Microtubules are found in all cells except red blood cells.

Structure

- cylindrical structure composed of alternating α and β tubulin subunits which polymerize to form protofilaments
- microtubules are polarized, having a positive and negative end

Molecular transport

- attachment proteins called dynein and kinesin move up and down the microtubules facilitating the movement of various organelles around the cell
- dynein moves in a retrograde fashion, down the the microtubule towards the centre of the cell (+ve → -ve)
- kinesin moves in an anterograde fashion, up the microtubule away from the centre, towards the periphery (-ve → +ve)

## MEMBRANE RECEPTORS

There are four main types of membrane receptor: ligand-gated ion channels, tyrosine kinase receptors, guanylate cyclase receptors and G protein-coupled receptors

Ligand-gated ion channel receptors

- generally mediate fast responses
- e.g. nicotinic acetylcholine, GABA-A & GABA-C, glutamate receptors

Tyrosine kinase receptors

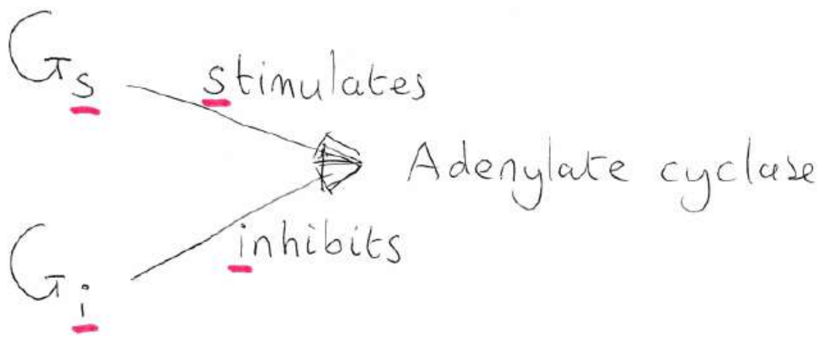
- receptor tyrosine kinase: insulin, insulin-like growth factor (IGF), epidermal growth factor (EGF)
- non-receptor tyrosine kinase: PIGG(L)ET: Prolactin, Immunomodulators (cytokines IL-2, Il-6, IFN), GH, G-CSF, Erythropoietin and Thromobopoietin

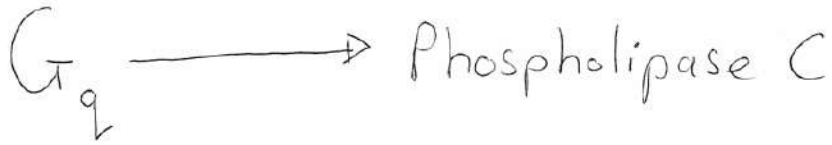
Guanylate cyclase receptors

- contain intrinsic enzyme activity
- e.g. atrial natriuretic factor, brain natriuretic peptide

G protein-coupled receptors

- generally mediate slow transmission and affect metabolic processes
- activated by a wide variety of extracellular signals e.g. Peptide hormones, biogenic amines, lipophilic hormones, light
- 7-helix membrane-spanning domains
- consist of 3 main subunits: alpha, beta and gamma
- the alpha subunit is linked to GDP.Ligand binding causes conformational changes to receptor, GDP is phosphorylated to GTP,and the alpha subunit is activated
- G proteins are named according to the alpha subunit (Gs, Gi, Gq)





| | **$G_s$** | **$G_i$** | **$G_q$** |
|---|---|---|---|
| **Mechanism** | Stimulates adenylate cyclase → increases cAMP → activates protein kinase A | Inhibits adenylate cyclase → decreases cAMP → inhibits protein kinase A | Activates phospholipase C → splits $PIP_2$ to $IP_3$ & DAG → activates protein kinase C |
| **Examples** | • Beta-1 receptors (epinephrine, norepinephrine, dobutamine)<br>• Beta-2 receptors (epinephrine, salbuterol)<br>• H2 receptors (histamine)<br>• D1 receptors (dopamine)<br>• V2 receptors (vasopressin)<br>• Receptors for ACTH, LH, FSH, glucagon, PTH, calcitonin, prostaglandins | • M2 receptors (acetylcholine)<br>• Alpha-2 receptors (epinephrine, norephinephrine)<br>• D2 receptors (dopamine)<br>• GABA-B receptor | • Alpha-1 receptors (epinephrine, norepinephrine)<br>• H1 receptors (histamine)<br>• V1 receptors (vasopressin)<br>• M1, M3 receptors (acetylcholine) |

## CELL SURFACE PROTEINS

The table below shows the most common cell surface proteins associated with particular cell types:

| Type of cell | Cell surface markers |
|---|---|
| Haematopoietic stem cells | CD34 |
| Helper T cell | CD4, TCR, CD3, CD28 |
| Cytotoxic T cell | CD8, TCR, CD3, CD28 |

| Type of cell | Cell surface markers |
|---|---|
| Regulatory T cell | CD4, CD25, TCR, CD3, CD28 |
| B cell | CD19, CD20, CD40, MHC II, B7 |
| Macrophage | CD14, CD40, MHC II, B7 |
| Natural killer cell | CD16, CD56 |

The table below lists the major clusters of differentiation (CD) molecules and describes their function.

| Cluster of differentiation | Function |
|---|---|
| CD1 | MHC molecule that presents lipid molecules |
| CD2 | Found on thymocytes, T cells, and some natural killer cells that acts as a ligand for CD58 and CD59 and is involved in signal transduction and cell adhesion |
| CD3 | The signalling component of the T cell receptor (TCR) complex |
| CD4 | Found on helper T cells.<br>Co-receptor for MHC class II<br>Used by HIV to enter T cells |
| CD5 | Found in the majority of mantle cell lymphomas |
| CD8 | Found on cytotoxic T cells.<br>Co-receptor for MHC class I<br>Found on a subset of myeloid dendritic cells |
| CD14 | Cell surface marker for macrophages |
| CD15 | Expressed on Reed-Sternberg cells (along with CD30) |
| CD16 | Bind to the Fc portion of IgG antibodies |
| CD21 | Receptor for Epstein-Barr virus |
| CD28 | Interacts with B7 on antigen presenting cell as costimulation signal |
| CD45 | Protein tyrosine phosphatase present on all leucocytes |
| CD56 | Unique marker for natural killer cells |
| CD95 | Acts as the FAS receptor, involved in apoptosis |

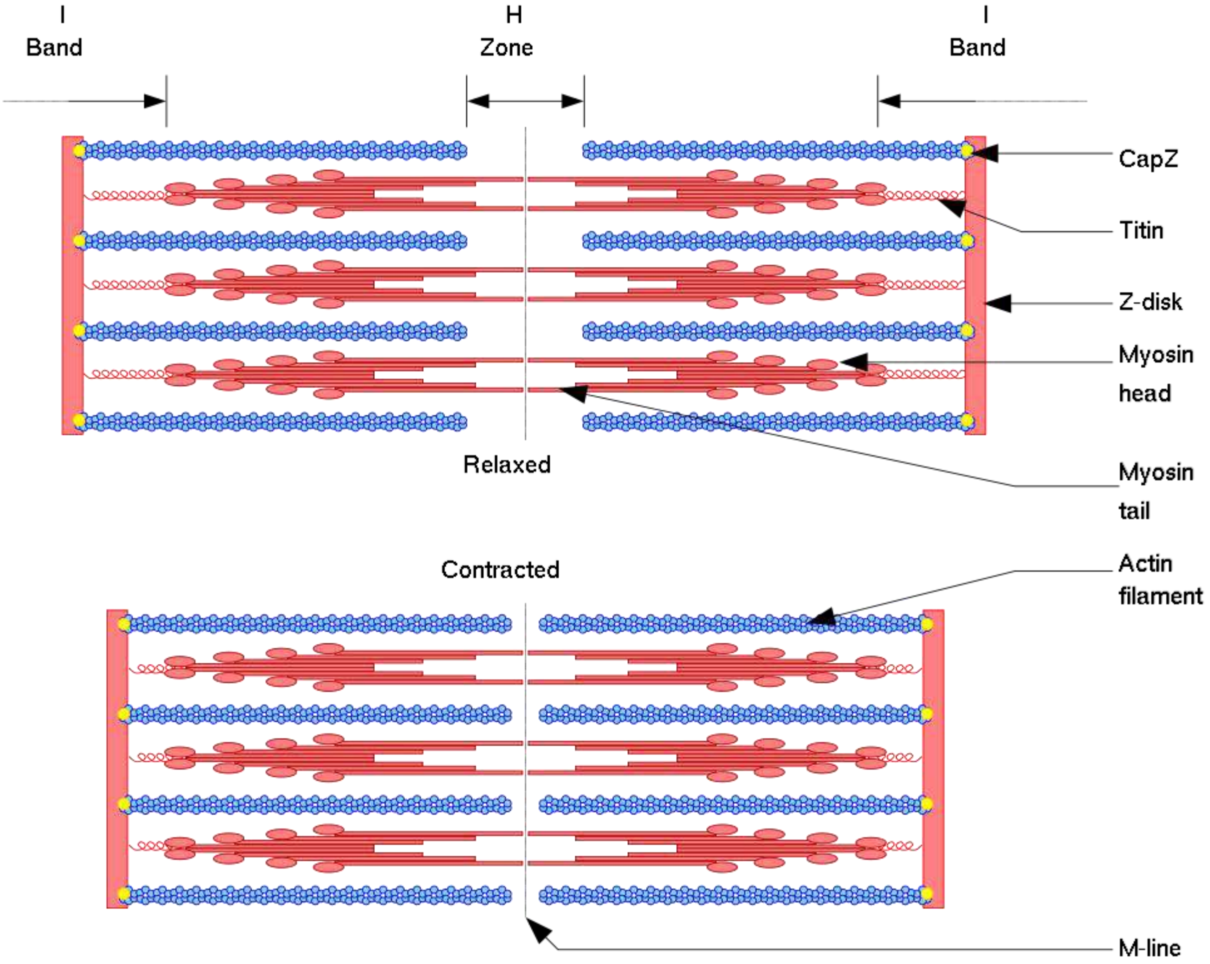
# MUSCLE CONTRACTION

### Skeletal muscle contraction

Major steps:

- action potential reaches the neuromuscular junction, causing a calcium ion influx through voltage-gated calcium channels
- the calcium influx causes the release of acetylcholine into the extracellular space
- the acetylcholine activates nicotinic acetylcholine receptors causing an influx of sodium, triggering an action potential
- the action potential spreads through the T-tubules

- the depolarization activates L-type voltage-dependent calcium channels (dihydropyridine receptors) in the T-tubule membrane, which are close to calcium-release channels (ryanodine receptors) in the adjacent sarcoplasmic reticulum
- this causes the sarcoplasmic reticulum to release calcium
- calcium binds to troponin C (found on actin-containing thin filaments) causing a conformational change, allowing tropomyosin to move, unblocking the binding sites
- myosin binds to the newly released binding site releasing ADP, pulling the Z bands towards each other
- ATP binds to myosin, releasing actin



| Component | Notes |
|---|---|
| Sarcomere | Basic unit of muscles that gives skeletal and cardiac muscles their striated appearance. Segment between two adjacent Z-lines |
| I-band | Zone of thin filaments that is not superimposed by thick filaments |
| A-band | Contains the entire length of a single thick filament |
| H-zone | Zone of the thick filaments that is not superimposed by the thin filaments |
| M-line | Middle of the sarcomere, cross-linking myosin |
| Sarcoplasmic reticulum | Releases calcium ion in response to depolarization |
| Actin | Thin filaments that transmit the forces generated by myosin to the ends of the muscle |

| Component | Notes |
|---|---|
| Myosin | Thick filaments<br>Binds to thin filament |
| Titin | Connects the Z-line to the thick filament, altering the structure of tropomyosin |
| Tropomyosin | Covers the myosin-binding sites on actin |
| Troponin-C | Binds with calcium ions |
| T-tubule | Is an invagination of the sarcoplasmic reticulum<br>Helps co-ordinate muscular contraction |

The table below shows the types of skeletal muscle fibres (type II fibres are simplified into one category):

|  | Type I | Type II |
|---|---|---|
| **Contraction time** | Slow | Fast |
| **Colour** | Red (due to presence of myoglobin) | White (due to absence of myoglobin) |
| **Main use** | Sustained force | Sudden movement |
| **Major fuel** | Triglycerides | ATP |
| **Mitochondrial density** | High | Low |

Mnemonic for type I fibres - 'One Slow, Fat, Red Ox'

# TROPONIN

Troponin is a complex of three proteins involved in skeletal and cardiac muscle contraction

Subunits of troponin
troponin C: binds to calcium ions
troponin T: binds to tropomyosin, forming a troponin-tropomyosin complex
troponin I: binds to actin to hold the troponin-tropomyosin complex in place

# SECOND MESSENGERS

Overview

- many different types
- allow amplification of external stimulus

|  | cAMP system | Phosphoinositol system | cGMP system | Tyrosine kinase system |
|---|---|---|---|---|
| **Ligand: Neurotransmitters (Receptor)** | Epinephrine (α2, β1, β2)<br>Acetylcholine (M2) | Epinephrine (α1)<br>Acetylcholine (M1, M3) | - | - |

| | **cAMP system** | **Phosphoinositol system** | **cGMP system** | **Tyrosine kinase system** |
|---|---|---|---|---|
| **Ligand: Hormones** | ACTH, ADH, calcitonin, FSH, glucagon, hCG,LH, MSH, PTH, TSH, GHRH* | angiotensin II, GnRH, GHRH*, Oxytocin, TRH | ANP, Nitric oxide | insulin, growth hormone, IGF, PDGF |
| **Primary effector** | Adenylyl cyclase | Phospholipase C | Guanylate cyclase | Receptor tyrosine kinase |
| **Secondary messenger** | cAMP (cyclic adenosine monophosphate) | IP3 (inositol 1,4,5 trisphosphate) and DAG (Diacylglycerol) | cGMP | Protein phosphatase |

*the cAMP pathway is the most important

# CARDIOVASCULAR PHYSIOLOGY

### Left ventricular ejection fraction

Left ventricular ejection fraction = (stroke volume / end diastolic LV volume ) * 100%

Stroke volume = end diastolic LV volume - end systolic LV volume

### Cardiac output

Cardiac output = stroke volume x heart rate

### Pulse pressure

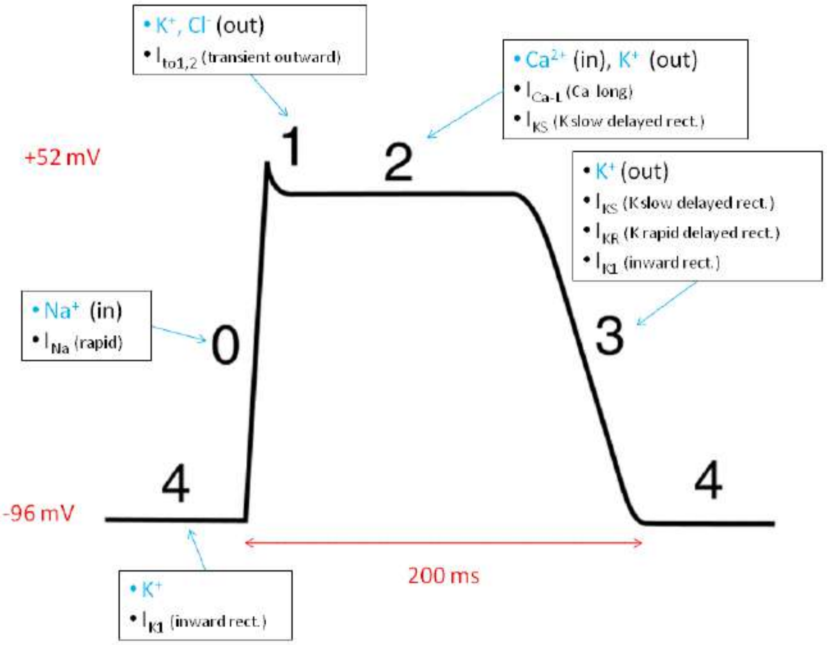
Pulse pressure = Systolic Pressure - Diastolic Pressure

Factors which increase pulse pressure
- a less compliant aorta (this tends to occur with advancing age)
- increased stroke volume

### Systemic vascular resistance

Systemic vascular resistance = mean arterial pressure / cardiac output

# CARDIAC ACTION POTENTIAL



$K^+$, $Cl^-$ (out)
$I_{to1,2}$ (transient outward)
$Ca^{2+}$ (in), $K^+$ (out)
$I_{Ca-L}$ (Ca long)
$I_{KS}$ (K slow delayed rect.)
+52 mV
1
2
$K^+$ (out)
$I_{KS}$ (K slow delayed rect.)
$I_{KR}$ (K rapid delayed rect.)
$I_{K1}$ (inward rect.)
$Na^+$ (in)
$I_{Na}$ (rapid)
0
3
4
-96 mV
4
200 ms
$K^+$
$I_{K1}$ (inward rect.)

| Phase | Description | Mechanism |
|---|---|---|
| 0 | Rapid depolarisation | Rapid sodium influx<br>These channels automatically deactivate after a few ms |
| 1 | Early repolarisation | Efflux of potassium |
| 2 | Plateau | Slow influx of calcium |
| 3 | Final repolarisation | Efflux of potassium |
| 4 | Restoration of ionic concentrations | Resting potential is restored by $Na^+/K^+$ ATPase<br>There is slow entry of $Na^+$ into the cell decreasing the potential difference until the threshold potential is reached, triggering a new action potential |

NB cardiac muscle remains contracted 10-15 times longer than skeletal muscle

**Conduction velocity**

| Site | Speed |
|---|---|
| Atrial conduction | Spreads along ordinary atrial myocardial fibres at 1 m/sec |
| AV node conduction | 0.05 m/sec |
| Ventricular conduction | Purkinje fibres are of large diameter and achieve velocities of 2-4 m/sec, the fastest conduction in the heart. This allows a rapid and coordinated contraction of the ventricles |

# ATRIAL NATRIURETIC PEPTIDE

Basics

- secreted mainly from myocytes of right atrium and ventricle in response to increased blood volume
- secreted by both the right and left atria (right >> left)
- 28 amino acid peptide hormone, which acts via cGMP
- degraded by endopeptidases

Actions

- natriuretic, i.e. promotes excretion of sodium
- lowers BP
- antagonises actions of angiotensin II, aldosterone

# NITRIC OXIDE

Previously known as endothelium derived relaxation factor, nitric oxide (NO) has emerged as a molecule which is integral to many physiological and pathological processes. It is formed from L-arginine and oxygen by nitric oxide synthetase (NOS). An inducible form of NOS has been shown to be present in macrophages. Nitric oxide has a very short half-life (seconds), being inactivated by oxygen free radicals

Effects
- acts on guanylate cyclase leading to raised intracellular cGMP levels and therefore decreasing $Ca^{2+}$ levels
- vasodilation, mainly venodilation
- inhibits platelet aggregation

Clinical relevance
- underproduction of NO is implicated in hypertrophic pyloric stenosis
- lack of NO is thought to promote atherosclerosis
- in sepsis increased levels of NO contribute to septic shock
- organic nitrates (metabolism produces NO) is widely used to treat cardiovascular disease (e.g. angina, heart failure)
- sildenafil is thought to potentiate the action of NO on penile smooth muscle and is used in the treatment of erectile dysfunctions

# ENDOTHELIN

Endothelin is a potent, long-acting vasoconstrictor and bronchoconstrictor. It is secreted initially as a prohormone by the vascular endothelium and later converted to ET-1 by the action of endothelin converting enzyme. It acts via interaction with a G-protein linked to phospholipase C leading to calcium release. Endothelin is thought to be important in the pathogenesis of many diseases including primary pulmonary hypertension (endothelin antagonists are now used), cardiac failure, hepatorenal syndrome and Raynaud's

Promotes release
- angiotensin II
- ADH
- hypoxia
- mechanical shearing forces

Inhibits release
- nitric oxide
- prostacyclin

Raised levels in
- MI

- heart failure
- ARF
- asthma
- primary pulmonary hypertension

# RESPIRATORY PHYSIOLOGY

Chloride shift

- $CO_2$ diffuses into RBCs
- $CO_2 + H_2O$ ---- carbonic anhydrase -→ $HCO_3^- + H^+$
- $H^+$ combines with Hb
- $HCO_3^-$ diffuses out of cell,- $Cl^-$ replaces it

Bohr effect

- increasing acidity (or $pCO_2$) means $O_2$ binds less well to Hb

Haldane effect

- increase $pO_2$ means $CO_2$ binds less well to Hb

# RESPIRATORY PHYSIOLOGY: CONTROL

Control of respiration

- central regulatory centres
- central and peripheral chemoreceptors
- pulmonary receptors

Central regulatory centres

- medullary respiratory centre
- apneustic centre (lower pons)
- pneumotaxic centre (upper pons)

Central and peripheral chemoreceptors

- central: raised $[H^+]$ in ECF stimulates respiration
- peripheral: carotid + aortic bodies, respond to raised $pCO_2$ & $[H^+]$, lesser extent low $pO_2$

Pulmonary receptors

- stretch receptors, lung distension causes slowing of respiratory rate (Hering-Bruer reflex)
- irritant receptor, leading to bronchoconstriction
- juxtacapillary receptors, stimulated by stretching of the microvasculature

# RESPIRATORY PHYSIOLOGY: LUNG COMPLIANCE

Lung compliance is defined as change in lung volume per unit change in airway pressure

Causes of increased compliance

- age
- emphysema - this is due to loss alveolar walls and associated elastic tissue

Causes of decreased compliance
- pulmonary oedema
- pulmonary fibrosis
- pneumonectomy
- kyphosis

# RESPIRATORY PHYSIOLOGY: HYPOXIA

A fall in the partial pressure of oxygen in the blood leads to vasoconstriction of the pulmonary arteries. This allows blood to be diverted to better aerated areas of the lung and improves the efficiency of gaseous exchange

# PULMONARY SURFACTANT

Surfactant is a mixture of phospholipids, carbohydrates and proteins released by type 2 pneumocytes. The main functioning component is dipalmitoyl phosphatidylcholine (DPPC) which reduces alveolar surface tension.

Basics
- first detectable around 28 weeks
- as alveoli decrease in size, surfactant concentration is increased, helping prevent the alveoli from collapsing
- reduces the muscular force needed to expand the lungs (i.e. decreases the work of breathing)
- lowers the elastic recoil at low lung volumes and thus helps to prevent the alveoli from collapsing at the end of each expiration

# GASTROINTESTINAL HORMONES

Below is a brief summary of the major hormones involved in food digestion:

| | Source | Stimulus | Actions |
|---|---|---|---|
| **Gastrin** | G cells in antrum of the stomach | Distension of stomach, vagus nerves (mediated by gastrin-releasing peptide), luminal peptides/amino acids<br>Inhibited by: low antral pH, somatostatin | Increase HCL, pepsinogen and IF secretion, increases gastric motility, stimulates parietal cell maturation |
| **CCK** | I cells in upper small intestine | Partially digested proteins and triglycerides | Increases secretion of enzyme-rich fluid from pancreas, contraction of gallbladder and relaxation of sphincter of Oddi, decreases gastric emptying, trophic effect on pancreatic acinar cells, induces satiety |
| **Secretin** | S cells in upper small intestine | Acidic chyme, fatty acids | Increases secretion of bicarbonate-rich fluid from pancreas and hepatic duct cells, decreases gastric acid secretion, trophic effect on pancreatic acinar cells |
| **VIP** | Small intestine, pancreas | Neural | Stimulates secretion by pancreas and intestines, inhibits acid secretion |
| **Somatostatin** | D cells in the pancreas & stomach | Fat, bile salts and glucose in the intestinal lumen | Decreases acid and pepsin secretion, decreases gastrin secretion, decreases pancreatic enzyme secretion, decreases insulin and glucagon secretion<br>inhibits trophic effects of gastrin, stimulates gastric mucous production |

# RENAL PHYSIOLOGY

Overview
- each nephron is supplied with blood from an afferent arteriole that opens onto the glomerular capillary bed
- blood then flows to an efferent arteriole, supplying the peritubular capillaries and medullary vasa recta
- the kidney receives up to 25% of resting cardiac output

Control of blood flow
- the kidney is able to autoregulate its blood flow between systolic pressures of 80-180mmHg so there is little variation in renal blood flow
- this is achieved by myogenic control of arteriolar tone, both sympathetic input and hormonal signals (e.g. renin) are responsible
- renal cortical blood flow > medullary blood flow (i.e. tubular cells more prone to ischaemia)

Glomerular structure and function
- blood inside the glomerulus has considerable hydrostatic pressure
- the basement membrane has pores that will allow free diffusion of smaller solutes, larger negatively charged molecules such as albumin are unable to cross
- the glomerular filtration rate (GFR) is equal to the concentration of a solute in the urine, times the volume of urine produced per minute, divided by the plasma concentration (assuming that the solute is freely diffused e.g. inulin)
- in clinical practice creatinine is used because it is subjected to very little proximal tubular secretion
- although subject to variability, the typical GFR is 125ml per minute
- glomerular filtration rate = Total volume of plasma per unit time leaving the capillaries and entering the Bowman's capsule
- renal clearance = volume plasma from which a substance is removed per minute by the kidneys

Substances used to measure GFR have the following features:
- Inert
- Free filtration from the plasma at the glomerulus (not protein bound)
- Not absorbed or secreted at the tubules
- Plasma concentration constant during urine collection
- examples: inulin, creatinine

GFR = ( urine concentration (mmol/l) x urine volume (ml/min) ) / plasma concentration (mmol/l)
- the clearance of a substance is dependent not only on its diffusivity across the basement membrane but also subsequent tubular secretion and / or reabsorption
- so glucose which is freely filtered across the basement membrane is usually reabsorbed from tubules giving a clearance of zero

Tubular function

- reabsorption and secretion of substances occurs in the tubules
- in the proximal tubule substrates such as glucose, amino acids and phosphate are co-transported with sodium across the semi permeable membrane
- up to two thirds of filtered water is reabsorbed in the proximal tubules
- this will lead to increase in urea concentration in the distal tubule allowing for its increased diffusion
- substances to be secreted into the tubules are taken up from the peritubular blood by tubular cells
- solutes such as para-aminohippuric acid are cleared with a single passage through the kidneys and this is why it is used to measure renal plasma flow. Ions such as calcium and phosphate will have a tubular reabsorption that is influenced by plasma PTH levels
- potassium may be both secreted and reabsorbed and is co-exchanged with sodium

Loop of Henle

- approximately 60 litres of water containing 9000mmol sodium enters the descending limb of the loop of Henle in 24 hours
- loops from the juxtamedullary nephrons run deep into the medulla
- the osmolarity of fluid changes and is greatest at the tip of the papilla
- the thin ascending limb is impermeable to water, but highly permeable to sodium and chloride ions
- this loss means that at the beginning of the thick ascending limb the fluid is hypo osmotic compared with adjacent interstitial fluid
- in the thick ascending limb the reabsorption of sodium and chloride ions occurs by both facilitated and passive diffusion pathways
- the loops of Henle are co-located with vasa recta, these will have similar solute compositions to the surrounding extracellular fluid so preventing the diffusion and subsequent removal of this hypertonic fluid
- the energy dependent reabsorption of sodium and chloride in the thick ascending limb helps to maintain this osmotic gradient

# RENIN

Renin is secreted by juxtaglomerular cells and hydrolyses angiotensinogen to produce angiotensin I

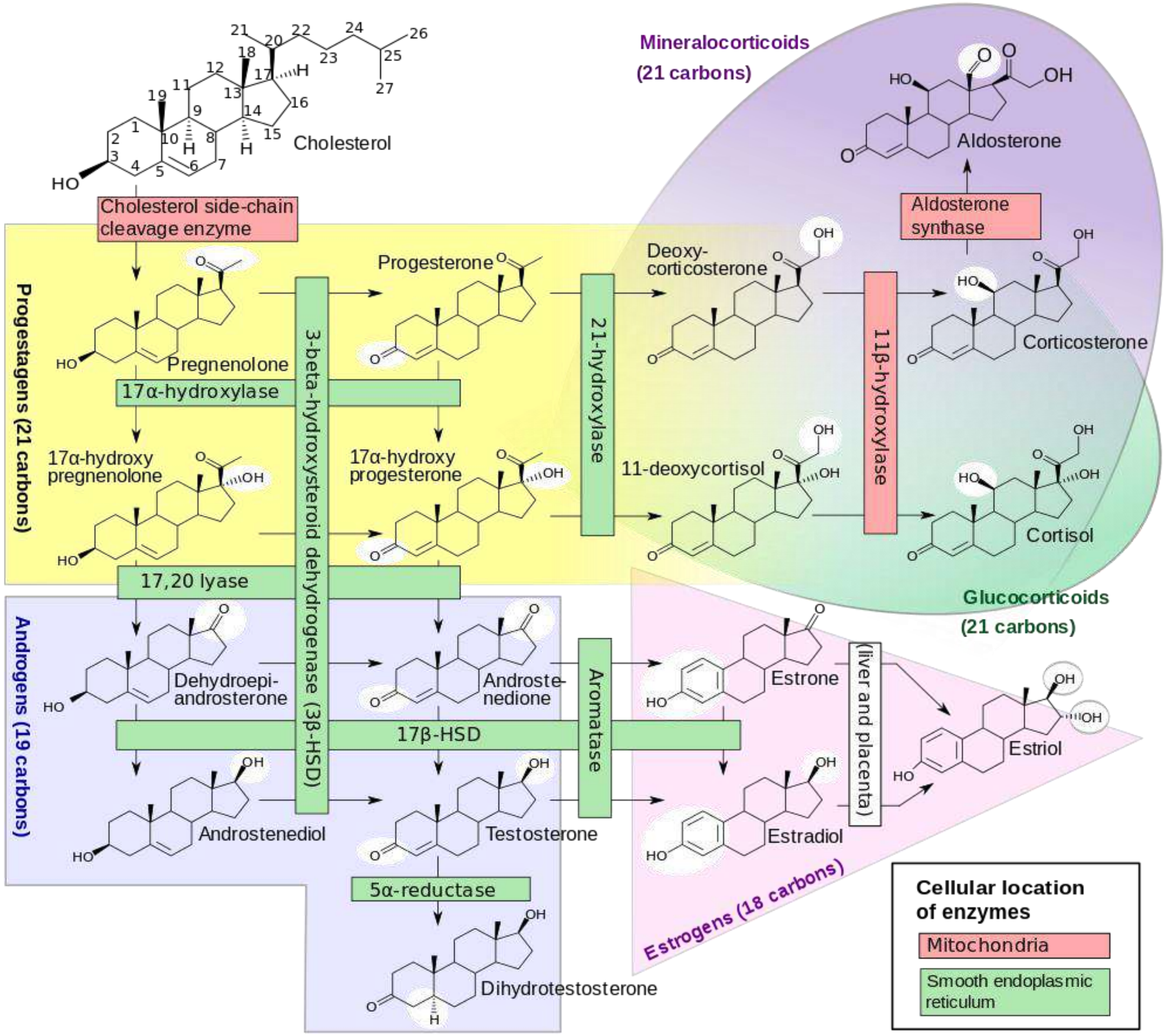
Factors stimulating renin secretion

- hypotension causing reduced renal perfusion
- hyponatraemia
- sympathetic nerve stimulation
- catecholamines
- erect posture

Factors reducing renin secretion
- drugs: beta-blockers, NSAIDs

# RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Adrenal cortex (mnemonic **GFR - ACD**)
- zona **g**lomerulosa (on outside): mineralocorticoids, mainly aldosterone
- zona **f**asciculata (middle): glucocorticoids, mainly cortisol
- zona **r**eticularis (on inside): androgens, mainly dehydroepiandrosterone (DHEA)



Cholesterol
Cholesterol side-chain cleavage enzyme
Mineralocorticoids (21 carbons)
Aldosterone
Aldosterone synthase
Progestagens (21 carbons)
Pregnenolone
Progesterone
Deoxy-corticosterone
Corticosterone
17α-hydroxylase
3-beta-hydroxysteroid dehydrogenase (3β-HSD)
21-hydroxylase
11β-hydroxylase
17α-hydroxy pregnenolone
17α-hydroxy progesterone
11-deoxycortisol
Cortisol
17,20 lyase
Glucocorticoids (21 carbons)
Androgens (19 carbons)
Dehydroepi-androsterone
Androste-nedione
Aromatase
Estrone
(liver and placenta)
Estriol
17β-HSD
Androstenediol
Testosterone
Estradiol
5α-reductase
Dihydrotestosterone
Estrogens (18 carbons)
Cellular location of enzymes
Mitochondria
Smooth endoplasmic reticulum

Renin

- an enzyme that **is released by the renal juxtaglomerular cells in response to reduced renal perfusion**
- other factors that stimulate renin secretion include hyponatraemia, sympathetic nerve stimulation
- hydrolyses angiotensinogen to form angiotensin I

Angiotensin II

- angiotensin-converting enzyme (ACE) in the lungs converts angiotensin I → angiotensin II
- angiotensin II has a wide variety of actions:
- causes **vasoconstriction of vascular smooth muscle** leading to raised blood pressure and **vasoconstriction of efferent arteriole of the glomerulus** → increased filtration fraction (FF) to preserve GFR. Remember that FF = GFR / renal plasma flow
- **stimulates thirst** (via the hypothalamus)
- **stimulates aldosterone and ADH** release
- **increases proximal tubule Na+/H+** activity

Aldosterone

- released by the zona glomerulosa in response to raised **angiotensin II, potassium, and ACTH levels**
- **causes retention of Na+** in exchange for K+/H+ in distal tubule

# ERYTHROPOIESIS

Erythropoiesis is the process through which red blood cells (erythrocytes) are produced. This occurs in red bone marrow found primarily in flat bones (including the vertebrae, ribs, and sternum) and the proximal ends of long bones in adults. In the foetus, erythrocytes are produced mainly in the liver.

Several components are required for erythropoiesis. Erythrocytes consist mainly of haemoglobin (Hb) which itself is composed of heme, containing iron to give the cell its oxygen-binding function, and globin protein. In addition, folate and vitamin B12 are required for cell division and DNA synthesis.

All types of blood cells are derived from haematopoietic stem cells. These differentiate into two types of precursor cells: lymphoid and myeloid. Erythrocytes originate from myeloid precursor cells.

Stages of differentiation in order of development:

| Cell type | Stage of differentiation |
|---|---|
| Haematocytoblast | Multipotent stem cell for all types of blood cells |
| Proerythroblast | Cell has become committed to its developmental pathway |

| Cell type | Stage of differentiation |
|---|---|
| Basophilic erythroblast | Ribosomes start to accumulate and the nucleus begins to shrink |
| Polychromatophilic erythroblast | Nucleus and total cell volume continue to shrink |
| Normoblast | Cell nucleus is ejected before developing further |
| Reticulocyte | Cells enter the circulation |
| Erythrocyte | Fully matured cell |

Erythropoiesis is regulated by erythropoietin (EPO), produced in the kidneys on detection of decreased oxygen levels in the circulation. This increases uptake of iron, heme biosynthesis, and globin gene transcription. Restored oxygen causes a negative feedback loop to the kidney to return to normal production.

Production of new erythrocytes takes around one week, and their lifespan is up to around 120 days.

Levels of erythrocytes are represented by the haematocrit, i.e. the percentage of blood volume occupied by erythrocytes. Erythropoiesis can be increased or decreased, changing the haematocrit. Dysfunctional bone marrow may produce too many erythrocytes (polycythaemia) or too few (anaemia). Low levels of any of the components of erythrocytes will also affect erythropoiesis, for example iron deficiency or pernicious anaemia (vitamin B12 deficiency).

# GROWTH HORMONE

Growth hormone (GH) is an anabolic hormone secreted by the somatotroph cells of the anterior lobe of the pituitary gland. It has actions on multiple organ systems and is important in postnatal growth and development. Growth hormone is also responsible for changes in protein, lipid, and carbohydrate metabolism

| | Notes | Further detail |
|---|---|---|
| **Source** | Anterior pituitary: Somatotrophs comprise 50% of the cells of the anterior pituitary gland | |
| **Function** | Postnatal growth and development<br>Numerous actions on protein, carbohydrate and fat metabolism (including increasing lipolysis and gluconeogenesis) | Mechanism of action<br>• acts on a transmembrane receptor for growth factor<br>• binding of GH to the receptor leads to receptor dimerization<br>• acts directly on tissues and also indirectly via insulin-like growth factor 1 (IGF-1), primarily secreted by the liver |
| **Regulation** | Increases secretion<br>• growth hormone releasing hormone (GHRH): released in pulses by the hypothalamus<br>• fasting<br>• exercise<br>• sleep (particularly delta sleep)<br>Decreases secretion<br>• glucose<br>• somatostatin (itself increased by somatomedins, circulating insulin-like growth factors, IGF-1 and IGF-2) | Conditions associated with GH disorders<br>▯ excess GH: acromegaly<br>▯ GH deficiency: resulting in short stature |

# ANTIDIURETIC HORMONE

Antidiuretic hormone (ADH) is secreted from the posterior pituitary gland. It promotes water reabsorption in the collecting ducts of the kidneys by the insertion of aquaporin-2 channels.

| | Notes | Further detail |
|---|---|---|
| **Source** | Synthesized in the supraoptic nuclei of the hypothalamus, released by the pituitary pituitary | |
| **Function** | Conserves body water | Promotes water reabsorption in the collecting ducts of the kidneys by the insertion of aquaporin-2 channels |
| **Regulation** | Increases secretion<br>• extracellular fluid osmolality increase<br>• volume decrease<br>• pressure decrease<br>• angiotensin II<br>Decreases secretion<br>• extracellular fluid osmolality decrease<br>• volume increase<br>• temperature decrease | Diabetes insipidus (DI) is a condition characterised by either a deficiency of antidiuretic hormone, ADH, (cranial DI) or an insensitivity to antidiuretic hormone (nephrogenic DI)<br>Cranial DI can be treated by desmopressin, an analog of ADH |

# PROLACTIN

| | Notes | Further detail |
|---|---|---|
| **Source** | Anterior pituitary | |
| **Function** | Stimulates breast development (both initially and further hyperplasia during pregnancy)<br>Stimulates milk production<br>It decreases GnRH pulsatility at the hypothalamic level and to a lesser extent, blocks the action of LH on the ovary or testis. | |
| **Regulation** | Prolactin secretion is under constant inhibition by dopamine<br>Increases secretion<br>• thyrotropin releasing hormone<br>• pregnancy<br>• oestrogen<br>• breastfeeding<br>• sleep | |

| | Notes | Further detail |
|---|---|---|
| | • stress<br>• drugs e.g. metoclopramide, antipsychotics<br>Decreases secretion<br>• dopamine<br>• dopaminergic agonists | |

# ADRENAL MEDULLA

The adrenal medulla secretes virtually all the adrenaline in the body as well as secreting small amounts of noradrenaline. It essentially represents an enlarged and specialised sympathetic ganglion

# CEREBRAL PERFUSION PRESSURE

The cerebral perfusion pressure (CPP) is defined as being the net pressure gradient causing blood flow to the brain. The CPP is tightly autoregulated to maximise cerebral perfusion. A sharp rise in CPP may result in a rising ICP, a fall in CPP may result in cerebral ischaemia. It may be calculated by the following equation:

CPP= Mean arterial pressure - Intra cranial pressure

Following trauma, the CPP has to be carefully controlled and the may require invasive monitoring of the ICP and MAP.

# ALKALINE PHOSPHATASE

Causes of raised alkaline phosphatase (ALP)

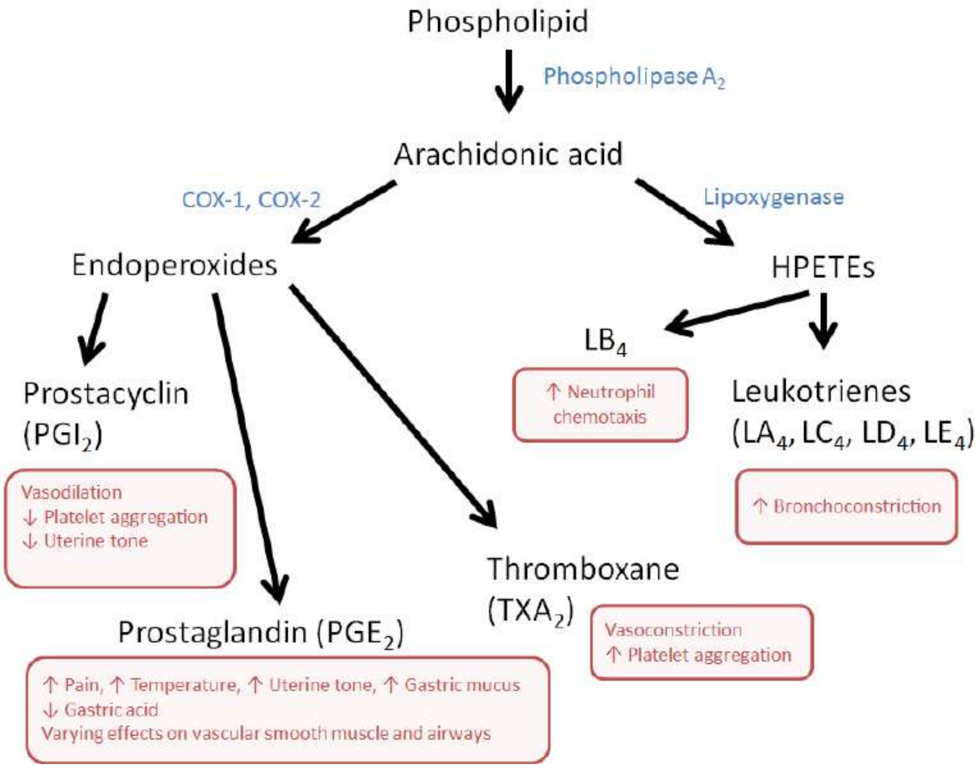
- liver: cholestasis, hepatitis, fatty liver, neoplasia
- Paget's
- osteomalacia
- bone metastases
- hyperparathyroidism
- renal failure
- physiological: pregnancy, growing children, healing fractures

The table below splits the causes according to the calcium level

| Raised ALP and raised calcium | Raised ALP and low calcium |
|---|---|
| Bone metastases | Osteomalacia |
| Hyperparathyroidism | Renal failure |

# ARACHIDONIC ACID METABOLISM

The diagram below shows the metabolism of arachidonic acid:



Phospholipid
Phospholipase $A_2$
Arachidonic acid
COX-1, COX-2
Lipoxygenase
Endoperoxides
HPETEs
$LB_4$
↑ Neutrophil chemotaxis
Leukotrienes ($LA_4$, $LC_4$, $LD_4$, $LE_4$)
↑ Bronchoconstriction
Prostacyclin ($PGI_2$)
Vasodilation
↓ Platelet aggregation
↓ Uterine tone
Thromboxane ($TXA_2$)
Vasoconstriction
↑ Platelet aggregation
Prostaglandin ($PGE_2$)
↑ Pain, ↑ Temperature, ↑ Uterine tone, ↑ Gastric mucus
↓ Gastric acid
Varying effects on vascular smooth muscle and airways

Leukotrienes

- LTB4: B4 (before) leukocytes comes LTB4
- the rest A, C, D & E constrict the lungs

Endoperoxides

- THROMBOxane think THROMBOSIS: platelets aggregated and vasoconstriction. Prostacyclin is the opposite

# IRON METABOLISM

Absorption

- upper small intestine especially the duodenum
- about 10% of dietary iron absorbed
- Fe2+ (ferrous iron) much better absorbed than Fe3+ (ferric iron)
- absorption is regulated according to body's need
- increased by vitamin C, gastric acid
- decreased by proton pump inhibitors, tetracycline, gastric achlorhydria, tannin (found in tea)

Distribution in body

- total body iron = 4g
- haemoglobin = 70%
- ferritin and haemosiderin = 25%
- myoglobin = 4%
- plasma iron = 0.1%

Transport

- carried in plasma as Fe3+ bound to transferrin

Storage

- stored as ferritin in tissues

Excretion

- lost via intestinal tract following desquamation

# FOLATE METABOLISM

Drugs which interfere with metabolism

- trimethoprim
- methotrexate
- pyrimethamine

Drugs which can reduce absorption

- phenytoin

# CALCIUM METABOLISM

The two hormones which primarily control calcium metabolism are:

- parathyroid hormone (PTH)
- 1,25-dihydroxycholecalciferol (calcitriol, the active form of vitamin D)

Other hormones include
- calcitonin: secreted from the parafollicular cells (C-cells) of the thyroid gland
- thyroxine
- growth hormone

Actions of parathyroid hormone
- increases plasma calcium, decreases plasma phosphate
- increases renal tubular reabsorption of calcium
- increases osteoclastic activity*
- increases renal conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol
- decreases renal phosphate reabsorption

Actions of 1,25-dihydroxycholecalciferol
- increases plasma calcium and plasma phosphate
- increases renal tubular reabsorption and gut absorption of calcium
- increases osteoclastic activity
- increases renal phosphate reabsorption

*this is actually via an indirect mechanism as osteoclasts don't have PTH receptors

# VITAMIN B1 (THIAMINE)

Thiamine is a water soluble vitamin of the B complex group. One of it's phosphate derivates, thiamine pyrophosphate (TPP), is a coenzyme in the following enzymatic reactions:
- pyruvate dehydrogenase complex
- pyruvate decarboxylase in ethanol fermentation
- alpha-ketoglutarate dehydrogenase complex
- branched-chain amino acid dehydrogenase complex
- 2-hydroxyphytanoyl-CoA lyase
- transketolase

Thiamine is therefore important in the catabolism of sugars and aminoacids. The clinical consequences of thiamine deficiency are therefore seen first in highly aerobic tissues such as the brain (Wenicke-Korsakoff syndrome) and the heart (wet beriberi).

Causes of thiamine deficiency:
- alcohol excess. Thiamine supplements are the only routinely recommend supplement in patients with alcoholism
- malnutrition

Conditions associated with thiamine deficiency:
- Wernicke's encephalopathy: nystagmus, ophthalmoplegia and ataxia
- Korsakoff's syndrome: amnesia, confabulation
- dry beriberi: peripheral neuropathy
- wet beriberi: dilated cardiomyopathy

# VITAMIN B2 (RIBOFLAVIN)

Riboflavin is a cofactor of flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) and is important in energy metabolism.

Consequences of riboflavin deficiency:
- angular cheilitis

# VITAMIN B3 (NIACIN)

Niacin is a water soluble vitamin of the B complex group. It is a precursor to NAD+ and NADP+ and hence plays an essential metabolic role in cells.

Biosynthesis
- Hartnup's disease: hereditary disorder which reduces absorption of tryptophan
- carcinoid syndrome: increased tryptophan metabolism to serotonin

Consequences of niacin deficiency:
- pellagra: dermatitis, diarrhoea, dementia

# VITAMIN B6 (PYRIDOXINE)

Vitamin B6 is a water soluble vitamin of the B complex group. It is converted to pyridoxal phosphate (PLP) which is a cofactor for many reactions including transamination, deamination and decarboxylation.

Causes of vitamin B6 deficiency
- isoniazid therapy

Consequences of vitamin B6 deficiency
- peripheral neuropathy
- sideroblastic anemia

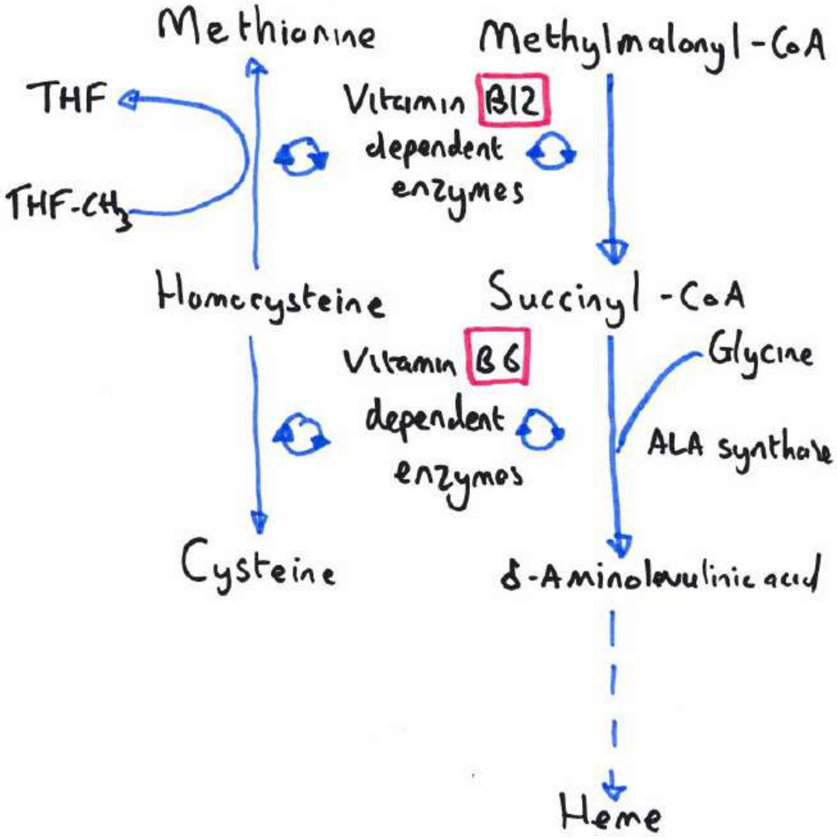

Methionine
Methylmalonyl-CoA
THF
Vitamin B12 dependent enzymes
THF-CH3
Homocysteine
Succinyl-CoA
Vitamin B6 dependent enzymes
Glycine
ALA synthase
Cysteine
δ-Aminolevulinic acid
Heme

Diagram showing the biochemical role of vitamin B12 and vitamin B6

## VITAMIN C (ASCORBIC ACID)

Vitamin C is a water soluble vitamin.

Functions

- antioxidant
- collagen synthesis: acts as a cofactor for enzymes that are required for the hydroxylation proline and lysine in the synthesis of collagen
- facilitates iron absorption
- cofactor for norepinephrine synthesis

Vitamin C deficiency (scurvy) leads to defective synthesis of collagen resulting in capillary fragility (bleeding tendency) and poor wound healing

Features vitamin C deficiency

- gingivitis, loose teeth
- poor wound healing
- bleeding from gums, haematuria, epistaxis
- general malaise

# VITAMIN C DEFICIENCY (SCURVY)

Vitamin C (ascorbic acid) is found in citrus fruits, tomatoes, potatoes, Brussel sprouts, cauliflower, broccoli, cabbage and spinach. Deficiency (commonly called scurvy) leads to impaired collagen synthesis and disordered connective tissue as ascorbic acid is a cofactor for enzymes used in the production of proline and lysine. It is associated with severe malnutrition as well as drug and alcohol abuse, and those living in poverty with limited access to fruits and vegetables.

Symptoms and signs include:
- Follicular hyperkeratosis and perifollicular haemorrhage
- Ecchymosis, easy bruising
- Poor wound healing
- Gingivitis with bleeding and receding gums
- Sjogren's syndrome
- Arthralgia
- Oedema
- Impaired wound healing
- Generalised symptoms such as weakness, malaise, anorexia and depression

# VITAMIN D

Vitamin D is a fat-soluble vitamin that plays a key role in calcium and phosphate metabolism. It is converted into the prohormone calcifediol in the liver. Circulating calcifediol is then converted into calcitriol (the biologically active form of vitamin D) in the kidneys.

Sources
- vitamin D2 (ergocalciferol): plants
- vitamin D3 (cholecalciferol): dairy products, can be synthesised by the skin from sunlight

Functions
- increases plasma calcium and plasma phosphate
- increases renal tubular reabsorption and gut absorption of calcium
- increases osteoclastic activity
- increases renal phosphate reabsorption

Consequences of vitamin D deficiency:
- rickets: seen in children
- osteomalacia: seen in adults

# RICKETS

Rickets is a term which describes inadequately mineralised bone in developing and growing bones. This results in soft and easily deformed bones. It is usually due to vitamin D deficiency. In adults the equivalent condition is termed osteomalacia

Predisposing factors
- dietary deficiency of calcium, for example in developing countries
- prolonged breast feeding
- unsupplemented cow's milk formula
- lack of sunlight

Features
- in toddlers - genu varum (bow legs), in older children - genu valgum (knock knees)
- 'rickety rosary' - swelling at the costochondral junction
- kyphoscoliosis
- craniotabes - soft skull bones in early life
- Harrison's sulcus
- reduced serum calcium - symptoms may results from hypocalcaemia
- raised alkaline phosphatase

Management
- oral vitamin D

# VITAMIN D-RESISTANT RICKETS

Vitamin D-resistant rickets is a X-linked dominant condition which usually presents in infancy with failure to thrive. It is caused by impaired phosphate reabsorption in the renal tubules

Features
- failure to thrive
- normal serum calcium, low phosphate, elevated alkaline phosphotase
- x-ray changes: cupped metaphyses with widening of the epiphyses

Diagnosis is made by demonstrating increased urinary phosphate

Management
- high-dose vitamin D supplements
- oral phosphate supplements

# VITAMIN K

Vitamin K is a fat-soluble vitamin which acts as a cofactor in the carboxylation of clotting factors (II, VII, IX, X).

Clinically, it is used to reverse the effects of warfarinisation
- takes up to 4 hours for there to be a change in the INR

Vitamin K deficiency
- as it is fat-soluble, vitamin K levels may fall in conditions affecting fat absorption
- deficiency may also occur after prolonged use of broad-spectrum antibiotics by eliminating the gut flora

# IMMUNE SYSTEM CELLS: INNATE IMMUNE RESPONSE

The following cells are mostly involved in the innate immune response:

| Cell type | Functions and properties |
|---|---|
| Neutrophil | Primary phagocytic cell in acute inflammation<br>Granules contain myeloperoxidase and lysozyme<br>Most common type of white blood cell<br>Multi-lobed nucleus |
| Basophil | Releases histamine during allergic response<br>Granules contain histamine and heparin<br>Expresses IgE receptors on the cell surface<br>Bi-lobed nucleus |
| Mast cell | Present in tissues and are similar in function to basophils but derived from different cell lines<br>Releases histamine during allergic response<br>Granules contain histamine and heparin<br>Expresses IgE receptors on the cell surface |
| Eosinophil | Defends against protozoan and helminthic infections<br>Bi-lobed nucleus |
| Monocyte | Diffferentiates into macrophages<br>Kidney shaped nucleus |
| Macrophage | Involved in phagocytosis of cellular debris and pathogens<br>Acts as an antigen presenting cell<br>Major source of IL-1 |
| Natural killer cell | Induce apoptosis in virally infected and tumour cells |
| Dendritic cell | Acts as an antigen presenting cell |

# IMMUNE SYSTEM CELLS: ADAPTIVE IMMUNE RESPONSE

The following cells are mostly involved in the adaptive immune response:

| Cell type | Functions and properties |
|---|---|
| Helper T cells | Involved in the cell-mediated immune response<br>Recognises antigens presented by MHC class II molecules<br>Expresses CD4<br>Also expresses CD3, TCR & CD28<br>Major source of IL-2<br>Mediates acute and chronic organ rejection |
| Cytotoxic T cells | Involved in the cell-mediated immune response<br>Recognises antigens presented by MHC class I molecules<br>Induce apoptosis in virally infected and tumour cells |

| Cell type | Functions and properties |
|---|---|
| | Expresses CD8<br>Also expresses CD3, TCR<br>Mediates acute and chronic organ rejection |
| B cells | Major cell of the humoral immune response<br>Acts as an antigen presenting cell<br>Mediates hyperacute organ rejection |
| Plasma cells | Differentiated from B cells<br>Produces large amounts of antibody specific to a particular antigen |

# IMMUNOGLOBULINS

The table below summarises the characteristics of the 5 types of immunoglobulin found in the body:

| Type | Frequency | Shape | Notes |
|---|---|---|---|
| **IgG** | 75% | Monomer | • Enhance phagocytosis of bacteria and viruses<br>• Fixes complement and passes to the fetal circulation<br>• Most abundant isotype in blood serum |
| **IgA** | 15% | Monomer/ dimer | • IgA is the predominant immunoglobulin found in breast milk. It is also found in the secretions of digestive, respiratory and urogenital tracts and systems<br>• Provides localized protection on mucous membranes<br>• Most commonly produced immunoglobulin in the body (but blood serum concentrations lower than IgG<br>.)<br>• Transported across the interior of the cell via transcytosis |
| **IgM** | 10% | Pentamer | • First immunoglobulins to be secreted in response to an infection<br>• Fixes complement but does not pass to the fetal circulation<br>• Anti-A, B blood antibodies (note how they cannot pass to the fetal circulation, which could of course result in haemolysis)<br>Pentamer when secreted |
| **IgD** | 1% | Monomer | • Role in immune system largely unknown<br>• Involved in activation of B cells |
| **IgE** | 0.1% | Monomer | • Mediates type 1 hypersensitivity reactions<br>• Binds to Fc receptors found on the surface of mast cells and basophils<br>• Provides immunity to parasites such as helminths<br>• Least abundant isotype in blood serum |

# T-HELPER CELLS

There are two major subsets of T-Helper cells:

Th1
- involved in the cell mediated response and delayed (type IV) hypersensitivity
- secrete IFN-gamma, IL-2, IL-3

Th2
- involved in mediating humoral (antibody) immunity
- e.g. stimulating production of IgE in asthma
- secrete IL-4, IL-5, IL-6, IL-10, IL-13

# CYTOKINES

### Interleukins

| Cytokine | Main sources | Functions |
|---|---|---|
| IL-1 | Macrophages | Acute inflammation<br>Induces fever |
| IL-2 | Th1 cells | Stimulates growth and differentiation of T cell response |
| IL-3 | Activated T helper cells | Stimulates differentiation and proliferation of myeloid progenitor cells |
| IL-4 | Th2 cells | Stimulates proliferation and differentiation of B cells |
| IL-5 | Th2 cells | Stimulate production of eosinophils |
| IL-6 | Macrophages, Th2 cells | Stimulates differentiation of B cells<br>Induces fever |
| IL-8 | Macrophages | Neutrophil chemotaxis |
| IL-10 | Th2 cells | Inhibits Th1 cytokine production<br>Also known as human cytokine synthesis inhibitory factor and is an 'anti-inflammatory' cytokine |
| IL-12 | Dendritic cells, macrophages, B cells | Activates NK cells and stimulates differentiation of naive T cells into Th1 cells |

### Other Cytokines

| Cytokine | Main sources | Functions |
|---|---|---|
| Tumour necrosis factor-α | Macrophages | Induces fever<br>Neutrophil chemotaxis |
| Interferon-γ | Th1 cells | Activates macrophages |

# IL-1

Interleukin 1 (IL-1) is a key mediator of the immune response. It is secreted mainly by macrophages and monocytes and acts as a costimulator of T cell and B cell proliferation.

Other effects include increasing the expression of adhesion molecules on the endothelium. By stimulating the release by the endothelium of vasoactive factors such as PAF, nitric oxide and prostacyclin it also causes vasodilation and increases vascular permeability. It is therefore one of the mediators of shock in sepsis. Along with IL-6 and TNF, it acts on the hypothalamus causing pyrexia.

## INTERFERON

Interferons (IFN) are cytokines released by the body in response to viral infections and neoplasia. They are classified according to cellular origin and the type of receptor they bind to. IFN-alpha and IFN-beta bind to type 1 receptors whilst IFN-gamma binds only to type 2 receptors.

Interferon-alpha

- produced by leucocytes
- antiviral action
- useful in hepatitis B & C, Kaposi's sarcoma, metastatic renal cell cancer, hairy cell leukaemia
- adverse effects include flu-like symptoms and depression

Interferon-beta

- produced by fibroblasts
- antiviral action
- reduces the frequency of exacerbations in patients with relapsing-remitting MS

Interferon-gamma

- predominately natural killer cells. Also by T helper cells
- weaker antiviral action, more of a role in immunomodulation particularly macrophage activation
- may be useful in chronic granulomatous disease and osteopetrosis

# LEUKOTRIENES

Function

- mediators of inflammation and allergic reactions
- cause bronchoconstriction, mucous production
- increase vascular permeability, attract leukocytes
- leukotriene D4 has been identified as the SRS-A (slow reacting substance of anaphylaxis)

Production

- secreted by leukocytes
- formed from arachidonic acid by action of lipoxygenase
- it is thought that the NSAID induced bronchospasm in asthmatics is secondary to the express production of leukotrienes due to the inhibition of prostaglandin synthetase

# ACUTE PHASE PROTEINS

Acute phase proteins

- CRP*
- procalcitonin
- ferritin
- fibrinogen
- alpha-1 antitrypsin
- caeruloplasmin
- serum amyloid A
- serum amyloid P component**
- haptoglobin
- complement

During the acute phase response the liver decreases the production of other proteins (sometimes referred to as negative acute phase proteins). Examples include:

- albumin
- transthyretin (formerly known as prealbumin)
- transferrin
- retinol binding protein
- cortisol binding protein

*Levels of CRP are commonly measured in acutely unwell patients. CRP is a protein synthesised in the liver and binds to phosphocholine in bacterial cells and on those cells undergoing apoptosis. In binding to these cells it is then able to activate the complement system. CRP levels are known to rise in patients following surgery. However, levels of greater than 150 at 48 hours post operatively are suggestive of evolving complications.

**plays a more significant role in other mammals such as mice

# HYPERSENSITIVITY

The Gell and Coombs classification divides hypersensitivity traditionally divides reactions into 4 types:

| Type | Mechanism | Examples |
|---|---|---|
| **Type I - Anaphylactic** | Antigen reacts with IgE bound to mast cells | • Anaphylaxis<br>• Atopy (e.g. asthma, eczema and hayfever) |
| **Type II - Cell bound** | IgG or IgM binds to antigen on cell surface | • Autoimmune haemolytic anaemia<br>• ITP<br>• Goodpasture's syndrome<br>• Pernicious anaemia<br>• Acute haemolytic transfusion reactions<br>• Rheumatic fever<br>• Pemphigus vulgaris / bullous pemphigoid |
| **Type III - Immune complex** | Free antigen and antibody (IgG, IgA) combine | • Serum sickness<br>• Systemic lupus erythematosus<br>• Post-streptococcal glomerulonephritis<br>• Extrinsic allergic alveolitis (especially acute phase) |
| **Type IV - Delayed hypersensitivity** | T-cell mediated | • Tuberculosis / tuberculin skin reaction<br>• Graft versus host disease<br>• Allergic contact dermatitis<br>• Scabies<br>• Extrinsic allergic alveolitis (especially chronic phase)<br>• Multiple sclerosis<br>• Guillain-Barre syndrome |

In recent times a further category has been added:

| Type | Mechanism | Examples |
|---|---|---|
| **Type V** | Antibodies that recognise and bind to the cell surface receptors.<br>This either stimulating them or blocking ligand binding | • Graves' disease<br>• Myasthenia gravis |

# MOLECULAR BIOLOGY TECHNIQUES

The following table shows a very basic summary of molecular biology techniques

| Technique | Description |
|---|---|
| Southern blotting | Detects DNA |
| Northern blotting | Detects RNA |
| Western blotting | Detects proteins<br>Uses gel electrophoresis to separate native proteins by 3-D structure<br>Examples include the **confirmatory** HIV test |

Molecular biology techniques

- SNOW (**S**outh - **NO**rth - **W**est)
- DROP (**D**NA - **R**NA - **P**rotein)

Enzyme-linked immunosorbent assay (ELISA)

- a type of biochemical assay used to detect antigens and antibodies
- a colour changing enzyme is attached to the antibody if looking for an antigen and to an antigen if looking for an antibody
- the sample therefore changes colour if the antigen or antibody is detected
- an example includes the **initial** HIV test

# POLYMERASE CHAIN REACTION

Polymerase chain reaction (PCR) is a molecular genetic investigation technique. The main advantage of PCR is its sensitivity: only one strand of sample DNA is needed to detect a particular DNA sequence. It now has many uses including prenatal diagnosis, detection of mutated oncogenes and diagnosis of infections. PCR is also extensively used in forensics. Prior to the procedure it is necessary to have two DNA oligonucleotide primers. These are complimentary to specific DNA sequences at either end of the target DNA

Initial prep

- sample of DNA is added to test tube along with two DNA primers
- a thermostable DNA polymerase (Taq) is added

The following cycle then takes place

- mixture is heated to almost boiling point causing denaturing (uncoiling) of DNA
- mixture is the allowed to cool: complimentary strands of DNA pair up, as there is an excess of the primer sequences they pair with DNA preferentially

The above cycle is then repeated, with the amount of DNA doubling each time

Reverse transcriptase PCR

- used to amplify RNA
- RNA is converted to DNA by reverse transcriptase
- gene expression in the form of mRNA (rather than the actually DNA sequence) can therefore be analyzed

# OBESITY: PHYSIOLOGY

### Leptin

Leptin is thought to play a key role in the regulation of body weight. It is produced by adipose tissue and acts on satiety centres in the hypothalamus and decreases appetite. More adipose tissue (e.g. in obesity) results in high leptin levels.

Leptin stimulates the release of melanocyte-stimulating hormone (MSH) and corticotrophin-releasing hormone (CRH). Low levels of leptin stimulates the release of neuropeptide Y (NPY)

### Ghrelin

Where as leptin induces satiety, ghrelin stimulates hunger. It is produced mainly by the P/D1 cells lining the fundus of the stomach and epsilon cells of the pancreas. Ghrelin levels increase before meals and decrease after meals

# SLEEP STAGES

| Sleep stage | EEG | Notes |
|---|---|---|
| Non-REM stage 1 (N1) | Theta waves | Light sleep<br>Transition to this stage be associated with hypnic jerks |
| Non-REM stage 2 (N2) | Sleep spindles + K-complexes | Deeper sleep<br>Represents around 50% of total sleep |
| Non-REM stage 3 (N3) | Delta waves | Deep sleep<br>Parasomnias such as night terrors, nocturnal enuresis, sleepwalking |
| REM | Beta-waves | Dreaming occurs<br>Loss of muscle tone, erections |

N1 → N2 → N3 → REM

**T**heta → **S**leep spindles/**K**-complexes → **D**elta → **B**eta

**T**he **S**leep **D**octor's **B**rain

# PENETRANCE AND EXPRESSIVITY

Not all patients with the same gene mutation (i.e. genotype) exhibit the same degree of observable characteristics (i.e. phenotype). This phenomenon is described using two terms - penetrance and expressivity. Penetrance describes the proportion of a population of individuals who carry a disease-causing allele who express the related disease phenotype. Expressivity describes the extent to which a genotype shows its phenotypic expression in an individual.

These phenomena are thought to be due to a number of factors, including:

- Modifier genes
- Environmental factors
- Allelic variation

Penetrance

- describes 'how likely' it is that a condition will develop
- examples of conditions with incomplete penetrance include retinoblastoma and Huntington's disease
- in contrast, achondroplasia shows 100%, or complete, penetrance

Expressivity

- describes the 'severity' of the phenotype
- a condition with a high level of expressivity is neurofibromatosis

# PHARMACOLOGY

## ANTIBIOTICS: MECHANISM OF ACTION

The lists below summarise the site of action of the commonly used antibiotics

Inhibit cell wall formation (beta-lactams)
- penicillins: binds transpeptidase blocking cross-linking of peptidoglycan cell walls
- cephalosporins

Inhibit protein synthesis: these antibiotics are bateriostatic
- aminoglycosides (cause misreading of mRNA)
- chloramphenicol
- macrolides (e.g. erythromycin)
- tetracyclines
- fusidic acid

Inhibit DNA synthesis
- quinolones (e.g. ciprofloxacin)
- metronidazole
- sulphonamides
- trimethoprim

Inhibit RNA synthesis
- rifampicin

## ANTIBIOTICS: PROTEIN SYNTHESIS INHIBITORS

| Drug | Mechanism of action | Adverse effects | Notes |
|---|---|---|---|
| Aminoglycosides | Binds to 30S subunit causing misreading of mRNA | Nephrotoxicity, Ototoxicity | |
| Tetracyclines | Binds to 30S subunit blocking binding of aminoacyl-tRNA | Discolouration of teeth, photosensitivity | |
| Chloramphenicol | Binds to 50S subunit, inhibiting peptidyl transferase | Aplastic anaemia | |
| Clindamycin | Binds to 50S subunit, inhibiting translocation (movement of tRNA from acceptor site to peptidyl site) | Common cause of *C. difficile* diarrhoea | |

| Drug | Mechanism of action | Adverse effects | Notes |
|---|---|---|---|
| Macrolides | Binds to 50S subunit, inhibiting translocation (movement of tRNA from acceptor site to peptidyl site) | Nausea (especially erythromycin), P450 inhibitor, prolonged QT interval | Commonly used for patients who are allergic to penicillin |

# ANAESTHETIC AGENTS

The table below summarises some of the more commonly used IV induction agents

| Agent | Specific features |
|---|---|
| Propofol | • GABA receptor agonist<br>• Rapid onset of anaesthesia<br>• Pain on IV injection<br>• Rapidly metabolised with little accumulation of metabolites<br>• Proven anti emetic properties<br>• Moderate myocardial depression<br>• Widely used especially for maintaining sedation on ITU, total IV anaesthesia and for daycase surgery |
| Sodium thiopentone | • Extremely rapid onset of action making it the agent of choice for rapid sequence of induction<br>• Marked myocardial depression may occur<br>• Metabolites build up quickly<br>• Unsuitable for maintenance infusion<br>• Little analgesic effects |
| Ketamine | • NMDA receptor antagonist<br>• May be used for induction of anaesthesia<br>• Has moderate to strong analgesic properties<br>• Produces little myocardial depression making it a suitable agent for anaesthesia in those who are haemodynamically unstable<br>• May induce state of dissociative anaesthesia resulting in nightmares |
| Etomidate | • Has favorable cardiac safety profile with very little haemodynamic instability<br>• No analgesic properties<br>• Unsuitable for maintaining sedation as prolonged (and even brief) use may result in adrenal suppression<br>• Post operative vomiting is common |

# LOCAL ANAESTHETIC AGENTS

Lidocaine

- An amide
- Local anaesthetic and a less commonly used antiarrhythmic (affects Na channels in the axon)
- Hepatic metabolism, protein bound, renally excreted
- Toxicity: due to IV or excess administration. Increased risk if liver dysfunction or low protein states. Note acidosis causes lidocaine to detach from protein binding. Local anesthetic toxicity can be treated with IV 20% lipid emulsion
- Drug interactions: Beta blockers, ciprofloxacin, phenytoin
- Features of toxicity: Initial CNS over activity then depression as lidocaine initially blocks inhibitory pathways then blocks both inhibitory and activating pathways. Cardiac arrhythmias.
- Increased doses may be used when combined with adrenaline to limit systemic absorption.

**Cocaine**

- Pure cocaine is a salt, usually cocaine hydrochloride. It is supplied for local anaesthetic purposes as a paste.
- It is supplied for clinical use in concentrations of 4 and 10%. It may be applied topically to the nasal mucosa. It has a rapid onset of action and has the additional advantage of causing marked vasoconstriction.
- It is lipophillic and will readily cross the blood brain barrier. Its systemic effects also include cardiac arrhythmias and tachycardia.
- Apart from its limited use in ENT surgery it is otherwise used rarely in mainstream surgical practice.

Bupivacaine

- Bupivacaine binds to the intracellular portion of sodium channels and blocks sodium influx into nerve cells, which prevents depolarization.
- It has a much longer duration of action than lignocaine and this is of use in that it may be used for topical wound infiltration at the conclusion of surgical procedures with long duration analgesic effect.
- It is cardiotoxic and is therefore contra indicated in regional blockage in case the tourniquet fails.
- Levobupivicaine (Chirocaine) is less cardiotoxic and causes less vasodilation.

**Prilocaine**

- Similar mechanism of action to other local anaesthetic agents. However, it is far less cardiotoxic and is therefore the agent of choice for intravenous regional anaesthesia e.g. Biers Block.

All local anaesthetic agents dissociate in tissues and this contributes to their therapeutic effect. The dissociation constant shifts in tissues that are acidic e.g. where an abscess is present, and this reduces the efficacy.

**Doses of local anaesthetics**

| Agent | Dose plain | Dose with adrenaline |
|---|---|---|
| Lignocaine | 3mg/Kg | 7mg/Kg |
| Bupivacaine | 2mg/Kg | 2mg/Kg |
| Prilocaine | 6mg/Kg | 9mg/Kg |

These are a guide only as actual doses depend on site of administration, tissue vascularity and co-morbidities.

**Maximum total local anaesthetic doses**

- Lignocaine 1% plain - 3mg/ Kg - 200mg (20ml)
- Lignocaine 1% with 1 in 200,000 adrenaline - 7mg/Kg - 500mg (50ml)
- Bupivicaine 0.5% - 2mg/kg- 150mg (30ml)

*Maximum doses are based on ideal body weight*

**Effects of adrenaline**

Adrenaline may be added to local anaesthetic drugs. It prolongs the duration of action at the site of injection and permits usage of higher doses (see above). It is contra indicated in patients taking MAOI's or tricyclic antidepressants. The toxicity of bupivacaine is related to protein binding and addition of adrenaline to this drug does not permit increases in the total dose of bupivacaine, in contrast to the situation with lignocaine.

# MUSCLE RELAXANTS

| | |
|---|---|
| **Suxamethonium** | • Depolarising neuromuscular blocker<br>• Inhibits action of acetylcholine at the neuromuscular junction<br>• Degraded by plasma cholinesterase and acetylcholinesterase<br>• Fastest onset and shortest duration of action of all muscle relaxants<br>• Produces generalised muscular contraction prior to paralysis<br>• Adverse effects include hyperkalaemia, malignant hyperthermia and lack of acetylcholinesterase |
| **Atracurium** | • Non depolarising neuromuscular blocking drug<br>• Duration of action usually 30-45 minutes<br>• Generalised histamine release on administration may produce facial flushing, tachycardia and hypotension<br>• Not excreted by liver or kidney, broken down in tissues by hydrolysis<br>• Reversed by neostigmine |
| **Vecuronium** | • Non depolarising neuromuscular blocking drug<br>• Duration of action approximately 30 - 40 minutes<br>• Degraded by liver and kidney and effects prolonged in organ dysfunction<br>• Effects may be reversed by neostigmine |
| **Pancuronium** | • Non depolarising neuromuscular blocker<br>• Onset of action approximately 2-3 minutes<br>• Duration of action up to 2 hours<br>• Effects may be partially reversed with drugs such as neostigmine |

# POST OPERATIVE FLUID MANAGEMENT

**Composition of commonly used intravenous fluids mmol-1**

| | Na | K | Cl | Bicarbonate | Lactate |
|---|---|---|---|---|---|
| Plasma | 137-147 | 4-5.5 | 95-105 | 22-25 | - |
| 0.9% Saline | 153 | - | 153 | - | - |
| Dextrose / saline | 30.6 | - | 30.6 | - | - |
| Hartmans | 130 | 4 | 110 | - | 28 |

**Post operative fluid management**

In the UK the GIFTASUP guidelines (see reference below) were devised to try and provide some consensus guidance as to how intravenous fluids should be administered. A decade ago it was a commonly held belief that little harm would occur as a result of excessive administration of normal saline and many oliguric postoperative patients received enormous quantities of IV fluids. As a result, they developed hyperchloraemic acidosis. With a greater understanding of this potential complication, the use of electrolyte balanced solutions (Ringers lactate/ Hartmans) is now favoured over normal saline. In addition to this, solutions of 5% dextrose and dextrose/saline combinations are now generally not recommended for surgical patients. The other guidance includes:

- Fluids given should be documented clearly and easily available
- Assess the patient's fluid status when they leave theatre
- If a patient is haemodynamically stable and euvolaemic, aim to restart oral fluid intake as soon as possible
- Review patients whose urinary sodium is < 20
- If a patient is oedematous, hypovolaemia if present should be treated first. This should then be followed by a negative balance of sodium and water, monitored using urine Na excretion levels.
- Solutions such as Dextran 70 should be used in caution in patients with sepsis as there is a risk of developing acute renal injury.

**References**

British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients
GIFTASUP (2009)

## POTASSIUM SPARING DIURETICS

Potassium-sparing diuretics may be divided into the epithelial sodium channel blockers (amiloride and triamterene) and aldosterone antagonists (spironolactone and eplerenone).

Amiloride is a weak diuretic which blocks the epithelial sodium channel in the distal convoluted tubule.

Usually given with thiazides or loop diuretics as an alternative to potassium supplementation.

Spironolactone is an aldosterone antagonist which acts act in the distal convoluted tubule.

Indications
- ascites: patients with cirrhosis develop a secondary hyperaldosteronism. Relatively large doses such as 100 or 200mg are often used
- heart failure
- nephrotic syndrome
- Conn's syndrome

## FIBRATES

Fibrates are used in the management of hyperlipidaemia, particularly raised triglycerides.

Fibrates work through activating PPAR alpha receptors resulting in an increase in LPL activity reducing triglyceride levels.

Adverse effects:
- gastrointestinal side-effects are common
- increased risk of thromboembolism

## EZETIMIBE

Ezetimibe is a lipid-lowering drug which inhibits cholesterol receptors on enterocytes, decreasing cholesterol absorption in the small intestine.

NICE produced guidelines in 2016 on the use of **ezetimibe in primary heterozygous-familial and non-familial hypercholesterolaemia**
- Ezetimibe monotherapy is recommended as an option for treating primary hypercholesterolaemia in adults in whom initial statin therapy is contraindicated or who cannot tolerate statin therapy

- Ezetimibe, coadministered with initial statin therapy, is recommended as an option for treating primary hypercholesterolaemia in adults who have started statin therapy when:
- → serum total or LDL cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy
- → a change from initial statin therapy to an alternative statin is being considered.

# BREASTFEEDING: CONTRAINDICATIONS

The major breastfeeding contraindications tested in exams relate to drugs (see below). Other contraindications of note include:
- galactosaemia
- viral infections - this is controversial with respect to HIV in the developing world. This is because there is such an increased infant mortality and morbidity associated with bottle feeding that some doctors think the benefits outweigh the risk of HIV transmission

**Drug contraindications**
The following drugs can be given to mothers who are breastfeeding:
- antibiotics: penicillins, cephalosporins, trimethoprim
- endocrine: glucocorticoids (avoid high doses), levothyroxine*
- epilepsy: sodium valproate, carbamazepine
- asthma: salbutamol, theophyllines
- psychiatric drugs: tricyclic antidepressants, antipsychotics**
- hypertension: beta-blockers, hydralazine
- anticoagulants: warfarin, heparin
- digoxin

The following drugs should be avoided:
- antibiotics: ciprofloxacin, tetracycline, chloramphenicol, sulphonamides
- psychiatric drugs: lithium, benzodiazepines
- aspirin
- carbimazole
- methotrexate
- sulfonylureas
- cytotoxic drugs
- amiodarone

*the BNF advises that the amount is too small to affect neonatal hypothyroidism screening

**clozapine should be avoided

# PATHOLOGY

## MITOCHONDRIAL DISEASES

Whilst most DNA is found in the cell nucleus, a small amount of double-stranded DNA is present in the mitochondria. It encodes protein components of the respiratory chain and some special types of RNA

Mitochondrial inheritance has the following characteristics:
- inheritance is only via the maternal line as the sperm contributes no cytoplasm to the zygote
- none of the children of an affected male will inherit the disease
- all of the children of an affected female will inherit the disease
- generally, encode rare neurological diseases
- poor genotype:phenotype correlation - within a tissue or cell there can be different mitochondrial populations - this is known as heteroplasmy

Histology
- muscle biopsy classically shows 'red, ragged fibres' due to increased number of mitochondria

Examples include:
- Leber's optic atrophy
- MELAS syndrome: mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes
- MERRF syndrome: myoclonus epilepsy with ragged-red fibres
- Kearns-Sayre syndrome: onset in patients < 20 years old, external ophthalmoplegia, retinitis pigmentosa. Ptosis may be seen
- sensorineural hearing loss

# COMPLEMENT DEFICIENCIES

Complement is a series of proteins that circulate in plasma and are involved in the inflammatory and immune reaction of the body. Complement proteins are involved in chemotaxis, cell lysis and opsonisation

C1 inhibitor (C1-INH) protein deficiency
- causes hereditary angioedema
- C1-INH is a multifunctional serine protease inhibitor
- probable mechanism is uncontrolled release of bradykinin resulting in oedema of tissues

C1q, C1rs, C2, C4 deficiency (classical pathway components)
- predisposes to immune complex disease
- e.g. SLE, Henoch-Schonlein Purpura

C3 deficiency
- causes recurrent bacterial infections

C5 deficiency
- predisposes to Leiner disease
- recurrent diarrhoea, wasting and seborrhoeic dermatitis

C5-9 deficiency
- encodes the membrane attack complex (MAC)
- particularly prone to Neisseria meningitidis infection

# PARATHYROID GLANDS AND DISORDERS OF CALCIUM METABOLISM

## Hyperparathyroidism

| Disease type | Hormone profile | Clinical features | Cause |
|---|---|---|---|
| Primary hyperparathyroidism | • PTH (Elevated)<br>• $Ca^{2+}$ (Elevated)<br>• Phosphate (Low)<br>• Urine calcium : creatinine clearance ratio > 0.01 |  May be asymptomatic if mild<br> Recurrent abdominal pain (pancreatitis, renal colic)<br> Changes to emotional or cognitive state | Most cases due to solitary adenoma (80%), multifocal disease occurs in 10-15% and parathyroid carcinoma in 1% or less |
| Secondary hyperparathyroidism | • PTH (Elevated)<br>• $Ca^{2+}$ (Low or normal)<br>• Phosphate (Elevated)<br>• Vitamin D levels (Low) |  May have few symptoms<br> Eventually may develop bone disease, osteitis fibrosa cystica and soft tissue calcifications | Parathyroid gland hyperplasia occurs as a result of low calcium, almost always in a setting of chronic renal failure |
| Tertiary hyperparathyroidism | • $Ca^{2+}$ (Normal or high)<br>• PTH (Elevated)<br>• Phosphate levels (Decreased or Normal)<br>• Vitamin D (Normal or decreased)<br>• Alkaline phosphatase (Elevated) |  Metastatic calcification<br> Bone pain and / or fracture<br> Nephrolithiasis<br> Pancreatitis | Occurs as a result of ongoing hyperplasia of the parathyroid glands after correction of underlying renal disorder, hyperplasia of all 4 glands is usually the cause |

## Differential diagnoses

It is important to consider the rare but relatively benign condition of benign familial hypocalciuric hypercalcaemia, caused by an autosomal dominant genetic disorder. Diagnosis is usually made by genetic testing and concordant biochemistry (urine calcium : creatinine clearance ratio <0.01- distinguished from primary hyperparathyroidism).

## Treatment

### Primary hyperparathyroidism

### Indications for surgery

- Elevated serum Calcium > 1mg/dL above normal
- Hypercalciuria > 400mg/day
- Creatinine clearance < 30% compared with normal
- Episode of life threatening hypercalcaemia
- Nephrolithiasis
- Age < 50 years
- Neuromuscular symptoms

- Reduction in bone mineral density of the femoral neck, lumbar spine, or distal radius of more than 2.5 standard deviations below peak bone mass (T score lower than -2.5)

**Secondary hyperparathyroidism**
*Usually managed with medical therapy.*

*Indications for surgery in secondary (renal) hyperparathyroidism:*
- Bone pain
- Persistent pruritus
- Soft tissue calcifications

**Tertiary hyperparathyroidism**
*Allow 12 months to elapse following transplant as many cases will resolve*
The presence of an autonomously functioning parathyroid gland may require surgery. If the culprit gland can be identified then it should be excised. Otherwise total parathyroidectomy and re-implantation of part of the gland may be required.

**References**

1. Pitt S et al. Secondary and Tertiary Hyperparathyroidism, State of the Art Surgical Management. Surg Clin North Am 2009 Oct;89(5):1227-39.

2. MacKenzie-Feder J et al. Primary Hyperparathyroidism: An Overview. Int J Endocrinol 2011; 2011: 251410.

# HUNGRY BONE SYNDROME

Hungry bone syndrome is an uncommon entity but can occur after parathyroidectomy if the hyperparathyroidism has been long-standing. The mechanism is thought to be thus: high pre-operative levels of parathyroid hormone provide a constant stimulus for osteoclast activity creating the hypercalcaemic state by de-mineralizing the bones. This process can result in x-ray changes very similar to metastatic lytic lesions if left untreated. Upon removal of the parathyroid adenoma the hormone levels fall rapidly (they have a very short half-life) and the osteoclast activity is subsequently diminished and the bones rapidly begin re-mineralisation - 'hungry bone syndrome'. This process can be uncomfortable and also result in systemic hypocalcaemia.

# DISORDERS OF SEX HORMONES

The table below summarises the findings in patients who have disorders of sex hormones:

| Disorder | LH | Testosterone |
|---|---|---|
| Primary hypogonadism (Klinefelter's syndrome) | High | Low |
| Hypogonadotrophic hypogonadism (Kallman's syndrome) | Low | Low |
| Androgen insensitivity syndrome | High | Normal/high |
| Testosterone-secreting tumour | Low | High |

**Klinefelter's syndrome**

Klinefelter's syndrome is associated with karyotype 47, XXY

Features
- often taller than average
- lack of secondary sexual characteristics
- small, firm testes
- infertile
- gynaecomastia - increased incidence of breast cancer
- elevated gonadotrophin levels

Diagnosis is by chromosomal analysis

**Kallman's syndrome**

Kallman's syndrome is a recognised cause of delayed puberty secondary to hypogonadotrophic hypogonadism. It is usually inherited as an X-linked recessive trait. Kallman's syndrome is thought to be caused by failure of GnRH-secreting neurons to migrate to the hypothalamus.

The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty

Features
- 'delayed puberty'
- hypogonadism, cryptorchidism
- anosmia
- sex hormone levels are low
- LH, FSH levels are inappropriately low/normal
- patients are typically of normal or above average height

Cleft lip/palate and visual/hearing defects are also seen in some patients

**Androgen insensitivity syndrome**

Androgen insensitivity syndrome is an X-linked recessive condition due to end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype. Complete androgen insensitivity syndrome is the new term for testicular feminisation syndrome

Features

- 'primary amenorrhoea'
- undescended testes causing groin swellings
- breast development may occur as a result of conversion of testosterone to oestradiol

Diagnosis

- buccal smear or chromosomal analysis to reveal 46XY genotype

Management

- counselling - raise child as female
- bilateral orchidectomy (increased risk of testicular cancer due to undescended testes)
- oestrogen therapy

# TURNER'S SYNDROME

Turner's syndrome is a chromosomal disorder affecting around 1 in 2,500 females. It is caused by either the presence of only one sex chromosome (X) or a deletion of the short arm of one of the X chromosomes. Turner's syndrome is denoted as 45,XO or 45,X.

Features

- short stature
- shield chest, widely spaced nipples
- webbed neck
- bicuspid aortic valve (15%), coarctation of the aorta (5-10%)
- primary amenorrhoea
- cystic hygroma (often diagnosed prenatally)
- high-arched palate
- short fourth metacarpal
- multiple pigmented naevi
- lymphoedema in neonates (especially feet)
- gonadotrophin levels will be elevated
- hypothyroidism is much more common in Turner's
- horseshoe kidney: the most common renal abnormality in Turner's syndrome

There is also an increased incidence of autoimmune disease (especially autoimmune thyroiditis) and Crohn's disease

# METABOLIC ALKALOSIS

Metabolic alkalosis may be caused by a loss of hydrogen ions or a gain of bicarbonate. It is due mainly to problems of the kidney or gastrointestinal tract

Causes
- vomiting / aspiration (e.g. peptic ulcer leading to pyloric stenos, nasogastric suction)
- diuretics
- liquorice, carbenoxolone
- hypokalaemia
- primary hyperaldosteronism
- Cushing's syndrome
- Bartter's syndrome

Mechanism of metabolic alkalosis
- activation of renin-angiotensin II-aldosterone (RAA) system is a key factor
- aldosterone causes reabsorption of Na+ in exchange for H+ in the distal convoluted tubule
- ECF depletion (vomiting, diuretics) → Na+ and Cl- loss → activation of RAA system → raised aldosterone levels
- in hypokalaemia, K+ shift from cells → ECF, alkalosis is caused by shift of H+ into cells to maintain neutrality

# HYPOCALCAEMIA: FEATURES

As extracellular calcium concentrations are important for muscle and nerve function many of the features seen in hypocalcaemia seen a result of neuromuscular excitability

Features
- tetany: muscle twitching, cramping and spasm
- perioral paraesthesia
- if chronic: depression, cataracts
- ECG: prolonged QT interval

Trousseau's sign
- carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- wrist flexion and fingers drawn together
- seen in around 95% of patients with hypocalcaemia and around 1% of normocalcaemic people

Chvostek's sign

- tapping over parotid causes facial muscles to twitch
- seen in around 70% of patients with hypocalcaemia and around 10% of normocalcaemic people

# HYPOCALCAEMIA: CAUSES AND MANAGEMENT

The clinical history combined with parathyroid hormone levels will reveal the cause of hypocalcaemia in the majority of cases

Causes

- vitamin D deficiency (osteomalacia)
- chronic kidney disease
- hypoparathyroidism (e.g. post thyroid/parathyroid surgery)
- pseudohypoparathyroidism (target cells insensitive to PTH)
- rhabdomyolysis (initial stages)
- magnesium deficiency (due to end organ PTH resistance)
- massive blood transfusion
- acute pancreatitis

Contamination of blood samples with EDTA may also give falsely low calcium levels.

Management

- acute management of severe hypocalcaemia is with intravenous replacement. The preferred method is with intravenous calcium gluconate, 10ml of 10% solution over 10 minutes
- intravenous calcium chloride is more likely to cause local irritation
- ECG monitoring is recommended
- further management depends on the underlying cause

# HYPERCALCAEMIA: MANAGEMENT

The initial management of hypercalcaemia is rehydration with normal saline, typically 3-4 litres/day. Following rehydration bisphosphonates may be used. They typically take 2-3 days to work with maximal effect being seen at 7 days

Other options include:

- calcitonin - quicker effect than bisphosphonates
- steroids in sarcoidosis

Loop diuretics such as furosemide are sometimes used in hypercalcaemia, particularly in patients who cannot tolerate aggressive fluid rehydration. However, they should be used with caution as they may worsen electrolyte derangement and volume depletion.

# HYPONATRAEMIA

Hyponatraemia may be caused by water excess or sodium depletion. Causes of pseudohyponatraemia include hyperlipidaemia (increase in serum volume) or a taking blood from a drip arm. Urinary sodium and osmolarity levels aid making a diagnosis

**Urinary sodium > 20 mmol/l**

Sodium depletion, renal loss (patient often hypovolaemic)
- diuretics: thiazides, loop diuretics
- Addison's disease
- diuretic stage of renal failure

Patient often euvolaemic
- SIADH (urine osmolality > 500 mmol/kg)
- hypothyroidism

**Urinary sodium < 20 mmol/l**

Sodium depletion, extra-renal loss
- diarrhoea, vomiting, sweating
- burns, adenoma of rectum

Water excess (patient often hypervolaemic and oedematous)
- secondary hyperaldosteronism: heart failure, liver cirrhosis
- nephrotic syndrome
- IV dextrose
- psychogenic polydipsia

# HYPONATRAEMIA: TREATMENT

Management of hyponatremia is primarily based around 2 parameters:
- Duration of hyponatremia
- Severity of hyponatremia and its symptoms

Acute hyponatremia:

- Develops over a period of less than 48 hours
- Usually from excessive fluid intake, either parenteral or oral. Common examples include post-operative parenteral fluids and athletes.
- Symptoms are usually severe.

Chronic hyponatremia:

- If the duration is unknown or it is present for more than 48 hours.
- Symptoms are usually less severe than acute.

| | **Mild hyponatremia** | **Moderate hyponatremia** | **Severe hyponatremia** |
|---|---|---|---|
| Serum Na+ | 130-134 mmol/l | 120-129 mmol/l | Less than 120 mmol/l |
| Symptoms | Non-specific symptoms such headache, lethargy, nausea, vomiting, dizziness, confusion, and muscle cramps | Same as mild | Seizures, coma, and respiratory arrest |
| Management | • Fluid restriction (less than 800 mL/day)<br>• Loop diuretics | ⍰ Hypertonic saline in first 3-4 hours to increase Na+ >120 mmol/l<br>⍰ Rest is the same as mild | ⍰ Bolus of hypertonic saline until symptom resolution<br>⍰ With or without conivaptan |

Fluids intake should be less than urine output in the following patients:

- Oedematous states like heart failure and cirrhosis
- SIADH
- Renal failure
- Psychogenic polydipsia

Vasopressin/ADH receptor antagonists (conivaptan):

- These act on V1 and V2 receptors. The V1 receptors cause vasoconstriction while the V2 receptors results in selective water diuresis, sparing the electrolytes.
- They should be avoided in patients who have hypovolemic hyponatremia.
- Vasopression/ADH receptor antagonists can stimulate the **thirst** receptors leading to the desire to drink free water. They can be **hepatotoxic** in patients with underlying liver disease.

Complications:

- **Osmotic demyelination syndrome (central pontine myelinolysis)** can occur due to over-correction of severe hyponatremia. To avoid this, Na+ levels are only raised by 4 to 6 mmol/l in a 24-hour period. Symptoms usually occur after 2 days and are usually irreversible. Dysarthria, dysphagia, paraparesis or quadriparesis, seizures, confusion, and coma. Patients are awake but are unable to move or verbally communicate, also called **'Locked-in syndrome'**

# SIADH: CAUSES

The syndrome of inappropriate ADH secretion (SIADH) is characterised by hyponatraemia secondary to the dilutional effects of excessive water retention.

Causes of SIADH

| Category | Examples |
|---|---|
| Malignancy | • **small cell lung cancer**<br>• also: pancreas, prostate |
| Neurological | • stroke<br>• subarachnoid haemorrhage<br>• subdural haemorrhage<br>• meningitis/encephalitis/abscess |
| Infections | • tuberculosis<br>• pneumonia |
| Drugs | • sulfonylureas*<br>• SSRIs, tricyclics<br>• carbamazepine<br>• vincristine<br>• cyclophosphamide |
| Other causes | • positive end-expiratory pressure (PEEP)<br>• porphyrias |

Management
- correction must be done slowly to avoid precipitating central pontine myelinolysis
- fluid restriction
- demeclocycline: reduces the responsiveness of the collecting tubule cells to ADH
- ADH (vasopressin) receptor antagonists have been developed

*the BNF states this has been reported with glimepiride and glipizide.

# HYPERNATRAEMIA

Causes of hypernatraemia
- dehydration
- osmotic diuresis e.g. hyperosmolar non-ketotic diabetic coma
- diabetes insipidus

- excess IV saline

Hypernatraemia should be corrected with great caution. Although brain tissue can lose sodium and potassium rapidly, lowering of other osmolytes (and importantly water) occurs at a slower rate, predisposing to cerebral oedema, resulting in seizures, coma and death1. Although there are no clinical guidelines by NICE or Royal College of Physicians at present, it is generally accepted that a rate of no greater than 0.5 mmol/hour correction is appropriate1.

1. Reynolds RM, Padfield PL, Seckl JR; Disorders of sodium balance. BMJ. 2006 Mar 25;332(7543):702-5.

# HYPOKALAEMIA

Potassium and hydrogen can be thought of as competitors. Hyperkalaemia tends to be associated with acidosis because as potassium levels rise fewer hydrogen ions can enter the cells

Hypokalaemia with alkalosis
- vomiting
- thiazide and loop diuretics
- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)

Hypokalaemia with acidosis
- diarrhoea
- renal tubular acidosis
- acetazolamide
- partially treated diabetic ketoacidosis

Magnesium deficiency may also cause hypokalaemia. In such cases, normalizing the potassium level may be difficult until the magnesium deficiency has been corrected

# HYPOKALAEMIA AND HYPERTENSION

For exams it is useful to be able to classify the causes of hypokalaemia in to those associated with hypertension, and those which are not

Hypokalaemia with hypertension
- Cushing's syndrome
- Conn's syndrome (primary hyperaldosteronism)
- Liddle's syndrome
- 11-beta hydroxylase deficiency*

Carbenoxolone, an anti-ulcer drug, and liquorice excess can potentially cause hypokalaemia associated with hypertension

Hypokalaemia without hypertension
- diuretics
- GI loss (e.g. Diarrhoea, vomiting)
- renal tubular acidosis (type 1 and 2**)
- Bartter's syndrome
- Gitelman syndrome

*21-hydroxylase deficiency, which accounts for 90% of congenital adrenal hyperplasia cases, is not associated with hypertension

**type 4 renal tubular acidosis is associated with hyperkalaemia

# PSEUDOHYPERKALAEMIA

Pseudohyperkalaemia is a rise in serum potassium that occurs due to excessive leakage of potassium from cells, during or after blood is taken. It is a laboratory artefact and does not represent the true serum potassium concentration. The majority of potassium is intracellular and thus leakage from cells can significantly impact serum levels. In this case the potassium is released as the large numbers of platelets aggregate and degranulate.

Causes include:
- haemolysis during venepuncture (excessive vacuum of blood drawing or too fine a needle gauge)
- delay in the processing of the blood specimen
- abnormally high numbers of platelets, leukocytes, or erythrocytes (such as myeloproliferative disorders)
- familial causes

Measuring an arterial blood gas will give a quick and accurate measure of true serum potassium. For obtaining a lab sample, using a lithium heparin tube, requesting a slow spin (on the lab centrifuge) and walking the sample to the lab should ensure an accurate result.

# HYPERKALAEMIA

Plasma potassium levels are regulated by a number of factors including aldosterone, acid-base balance and insulin levels. Metabolic acidosis is associated with hyperkalaemia as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule. ECG changes seen in hyperkalaemia include tall-tented T waves, small P waves, widened QRS leading to a sinusoidal pattern and asystole

Causes of hyperkalaemia:

- acute kidney injury
- drugs*: potassium sparing diuretics, ACE inhibitors, angiotensin 2 receptor blockers, spironolactone, ciclosporin, heparin**
- metabolic acidosis
- Addison's disease
- rhabdomyolysis
- massive blood transfusion

Foods that are high in potassium:

- salt substitutes (i.e. Contain potassium rather than sodium)
- bananas, oranges, kiwi fruit, avocado, spinach, tomatoes

*beta-blockers interfere with potassium transport into cells and can potentially cause hyperkalaemia in renal failure patients - remember beta-agonists, e.g. Salbutamol, are sometimes used as emergency treatment

**both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion

# HYPERURICAEMIA

Increased levels of uric acid may be seen secondary to either increased cell turnover or reduced renal excretion of uric acid. Hyperuricaemia may be found in asymptomatic patients who have not experienced attacks of gout

Hyperuricaemia may be associated with hyperlipidaemia and hypertension. It may also be seen in conjunction with the metabolic syndrome

Increased synthesis

- Lesch-Nyhan disease
- myeloproliferative disorders
- diet rich in purines
- exercise
- psoriasis
- cytotoxics

Decreased excretion

- drugs: low-dose aspirin, diuretics, pyrazinamide

- pre-eclampsia
- alcohol
- renal failure
- lead

# HYPOPHOSPHATAEMIA

Causes

- alcohol excess
- acute liver failure
- diabetic ketoacidosis
- refeeding syndrome
- primary hyperparathyroidism
- osteomalacia

Consequences

- red blood cell haemolysis
- white blood cell and platelet dysfunction
- muscle weakness and rhabdomyolysis
- central nervous system dysfunction

# HLA ASSOCIATIONS

HLA antigens are encoded for by genes on chromosome 6. HLA A, B and C are class I antigens whilst DP, DQ, DR are class II antigens. Questions are often based around which diseases have strong HLA associations. The most important associations are listed below:

HLA-A3
- haemochromatosis

HLA-B51
- Behcet's disease

HLA-B27
- ankylosing spondylitis
- Reiter's syndrome
- acute anterior uveitis

HLA-DQ2/DQ8
- coeliac disease

HLA-DR2
- narcolepsy
- Goodpasture's

HLA-DR3
- dermatitis herpetiformis
- Sjogren's syndrome
- primary biliary cirrhosis

HLA-DR4
- type 1 diabetes mellitus*
- rheumatoid arthritis - in particular the DRB1 gene (DRB1*04:01 and DRB1*04:04 hence the association with DR4)

*type 1 diabetes mellitus is associated with HLA-DR3 but is more strongly associated with HLA-DR4.

# AUTOSOMAL DOMINANT

In autosomal dominant diseases:

- both homozygotes and heterozygotes manifest disease (there is no carrier state)
- both males and females affected
- only affected individuals can pass on disease
- disease is passed on to 50% of children
- normally appears in every generation (although see below)
- risk remains same for each successive pregnancy

Complicating factors:

- non-penetrance: lack of clinical signs and symptoms (normal phenotype) despite abnormal gene. E.g. 40% otosclerosis
- spontaneous mutation: new mutation in one of gametes e.g. 80% of individuals with achondroplasia have unaffected parents

# AUTOSOMAL DOMINANT CONDITIONS

Autosomal recessive conditions are often thought to be 'metabolic' as opposed to autosomal dominant conditions being 'structural', notable exceptions:

- some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidaemia type II and hypokalaemic periodic paralysis are autosomal dominant
- some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive

The following conditions are autosomal dominant:

- Achondroplasia
- Acute intermittent porphyria
- Adult polycystic disease
- Antithrombin III deficiency
- Ehlers-Danlos syndrome
- Familial adenomatous polyposis
- Hereditary haemorrhagic telangiectasia
- Hereditary spherocytosis
- Hereditary non-polyposis colorectal carcinoma
- Huntington's disease
- Hyperlipidaemia type II
- Hypokalaemic periodic paralysis
- Malignant hyperthermia
- Marfan's syndromes
- Myotonic dystrophy

- Neurofibromatosis
- Noonan syndrome
- Osteogenesis imperfecta
- Peutz-Jeghers syndrome
- Retinoblastoma
- Romano-Ward syndrome
- tuberous sclerosis
- Von Hippel-Lindau syndrome
- Von Willebrand's disease*

*type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

# FAMILIAL HYPERCHOLESTEROLAEMIA

Familial hypercholesterolaemia (FH) is an autosomal dominant condition that is thought to affect around 1 in 500 people. It results in high levels of LDL-cholesterol which, if untreated, may cause early cardiovascular disease (CVD). FH is caused by mutations in the gene which encodes the LDL-receptor protein.

Case finding:

- NICE suggest that we should suspect FH as a possible diagnosis in adults with:
    - a total cholesterol level greater than 7.5 mmol/l and/or
    - a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative)
- children of affected parents:
    - if one parent is affected by familial hypercholesterolaemia, arrange testing in children by age 10
    - if both parents are affected by familial hypercholesterolaemia, arrange testing in children by age 5

Clinical diagnosis is now based on the **Simon Broome** criteria:

- in adults total cholesterol (TC) > 7.5 mmol/l and LDL-C > 4.9 mmol/l or children TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l, plus:
- for definite FH: tendon xanthoma in patients or 1st or 2nd degree relatives or DNA-based evidence of FH
- for possible FH: family history of myocardial infarction below age 50 years in 2nd degree relative, below age 60 in 1st degree relative, or a family history of raised cholesterol levels

Management

- the use of CVD risk estimation using standard tables is not appropriate in FH as they do not accurately reflect the risk of CVD

- referral to a specialist lipid clinic is usually required
- high-dose statins are usually used first-line
- first-degree relatives have a 50% chance of having the disorder and should therefore be offered screening. This includes children who should be screened by the age of 10 years if there is one affected parent
- statins should be discontinued in women 3 months before conception due to the risk of congenital defects

# ACHONDROPLASIA

Achondroplasia is an autosomal dominant disorder associated with short stature. It is caused by a mutation in the fibroblast growth factor receptor 3 (FGFR-3) gene. This results in abnormal cartilage giving rise to:

- short limbs (rhizomelia) with shortened fingers (brachydactyly)
- large head with frontal bossing and narrow foramen magnum
- midface hypoplasia with a flattened nasal bridge
- 'trident' hands
- lumbar lordosis

In most cases (approximately 70%) it occurs as a sporadic mutation. The main risk factor is advancing parental age at the time of conception. Once present it is typically inherited in an autosomal dominant fashion.

**Treatment**
There is no specific therapy. However, some individuals benefit from limb lengthening procedures. These usually involve application of Ilizarov frames and targeted bone fractures. A clearly defined need and end point is the cornerstone of achieving success with such procedures.

# AUTOSOMAL RECESSIVE CONDITIONS

Autosomal recessive conditions are often thought to be 'metabolic' as opposed to autosomal dominant conditions being 'structural', notable exceptions:

- some 'metabolic' conditions such as Hunter's and G6PD are X-linked recessive whilst others such as hyperlipidemia type II and hypokalemic periodic paralysis are autosomal dominant
- some 'structural' conditions such as ataxia telangiectasia and Friedreich's ataxia are autosomal recessive

The following conditions are autosomal recessive:

- Albinism
- Ataxic telangiectasia
- Congenital adrenal hyperplasia
- Cystic fibrosis
- Cystinuria
- Familial Mediterranean Fever
- Fanconi anaemia
- Friedreich's ataxia
- Gilbert's syndrome*
- Glycogen storage disease
- Haemochromatosis
- Homocystinuria
- Lipid storage disease: Tay-Sach's, Gaucher, Niemann-Pick
- Mucopolysaccharidoses: Hurler's
- PKU
- Sickle cell anaemia
- Thalassaemias
- Wilson's disease

*this is still a matter of debate and many textbooks will list Gilbert's as autosomal dominant

# CYSTIC FIBROSIS

Cystic fibrosis (CF) is an autosomal recessive disorder causing increased viscosity of secretions (e.g. lungs and pancreas). It is due to a defect in the cystic fibrosis transmembrane conductance regulator gene (CFTR), which codes a cAMP-regulated chloride channel

In the UK 80% of CF cases are due to delta F508 on the long arm of chromosome 7. Cystic fibrosis affects 1 per 2500 births, and the carrier rate is c. 1 in 25

Organisms which may colonise CF patients

- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- *Burkholderia cepacia**
- *Aspergillus*

*previously known as Pseudomonas cepacia

## CYSTIC FIBROSIS: FEATURES

Presenting features

- neonatal period (around 20%): meconium ileus, less commonly prolonged jaundice
- recurrent chest infections (40%)
- malabsorption (30%): steatorrhoea, failure to thrive
- other features (10%): liver disease

Whilst many patients are picked up during newborn screening programmes or early childhood, it is worth remembering that around 5% of patients are diagnosed after the age of 18 years.

Other features of cystic fibrosis

- short stature
- diabetes mellitus
- delayed puberty
- rectal prolapse (due to bulky stools)
- nasal polyps
- male infertility, female subfertility

## CYSTIC FIBROSIS: MANAGEMENT

Management of cystic fibrosis (CF) involves a multidisciplinary approach

Key points

- regular (at least twice daily) chest physiotherapy and postural drainage. Parents are usually taught to do this. Deep breathing exercises are also useful
- high calorie diet, including high fat intake*
- patients with CF should try to minimise contact with each other to prevent cross infection with Burkholderia cepacia complex and Pseudomonas aeruginosa
- vitamin supplementation
- pancreatic enzyme supplements taken with meals
- heart and lung transplant

Lumacaftor/Ivacaftor (Orkambi)
- is used to treat cystic fibrosis patients who are homozygous for the delta F508 mutation
- lumacaftor increases the number of CFTR proteins that are transported to the cell surface
- ivacaftor is a potentiator of CFTR that is already at the cell surface, increasing the probability that the defective channel will be open and allow chloride ions to pass through the channel pore

*this is now the standard recommendation - previously high calorie, low-fat diets have been recommended to reduce the amount of steatorrhoea

## GALACTOSAEMIA

Galactosaemia is a rare autosomal recessive condition caused by the absence of galactose-1-phosphate uridyl transferase. This results in intracellular accumulation of galactose-1-phosphate

Features
- jaundice
- failure to thrive
- hepatomegaly
- cataracts
- hypoglycaemia after exposure to galactose
- Fanconi syndrome

Diagnosis
- urine reducing substances

Management is with a galactose free diet

## HOMOCYSTINURIA

Homocystinuria is a rare autosomal recessive disease caused by a deficiency of cystathionine beta synthase. This results in severe elevations in plasma and urine homocysteine concentrations.

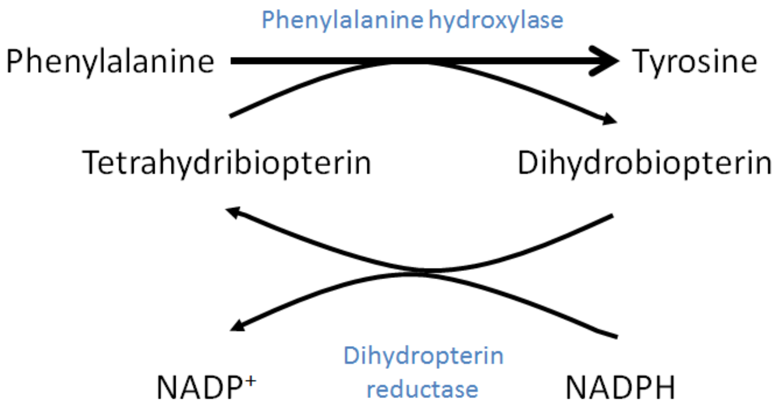
Features
- often patients have fine, fair hair
- musculoskeletal: may be similar to Marfan's - arachnodactyly etc
- neurological patients may have learning difficulties, seizures
- ocular: downwards (inferonasal) dislocation of lens
- increased risk of arterial and venous thromboembolism
- also malar flush, livedo reticularis

Diagnosis is made by the cyanide-nitroprusside test, which is also positive in cystinuria.

Treatment is vitamin B6 (pyridoxine) supplements.

## PHENYLKETONURIA

Phenylketonuria (PKU) is an autosomal recessive condition caused by a disorder of phenylalanine metabolism. This is usually due to defect in phenylalanine hydroxylase, an enzyme which converts phenylalanine to tyrosine. In a small number of cases the underlying defect is a deficiency of the tetrahydrobiopterin-deficient cofactor, e.g. secondary to defective dihydrobiopterin reductase. High levels of phenylalanine lead to problems such as learning difficulties and seizures. The gene for phenylalanine hydroxylase is located on chromosome 12. The incidence of PKU is around 1 in 10,000 live births.



Features

- usually presents by 6 months e.g. with developmental delay
- child classically has fair hair and blue eyes
- learning difficulties
- seizures, typically infantile spasms
- eczema
- 'musty' odour to urine and sweat*

Diagnosis

- Guthrie test: the 'heel-prick' test done at 5-9 days of life - also looks for other biochemical disorders such as hypothyroidism
- hyperphenylalaninaemia
- phenylpyruvic acid in urine

Management

- poor evidence base to suggest strict diet prevents learning disabilities

- dietary restrictions are however important during pregnancy as genetically normal fetuses may be affected by high maternal phenylalanine levels

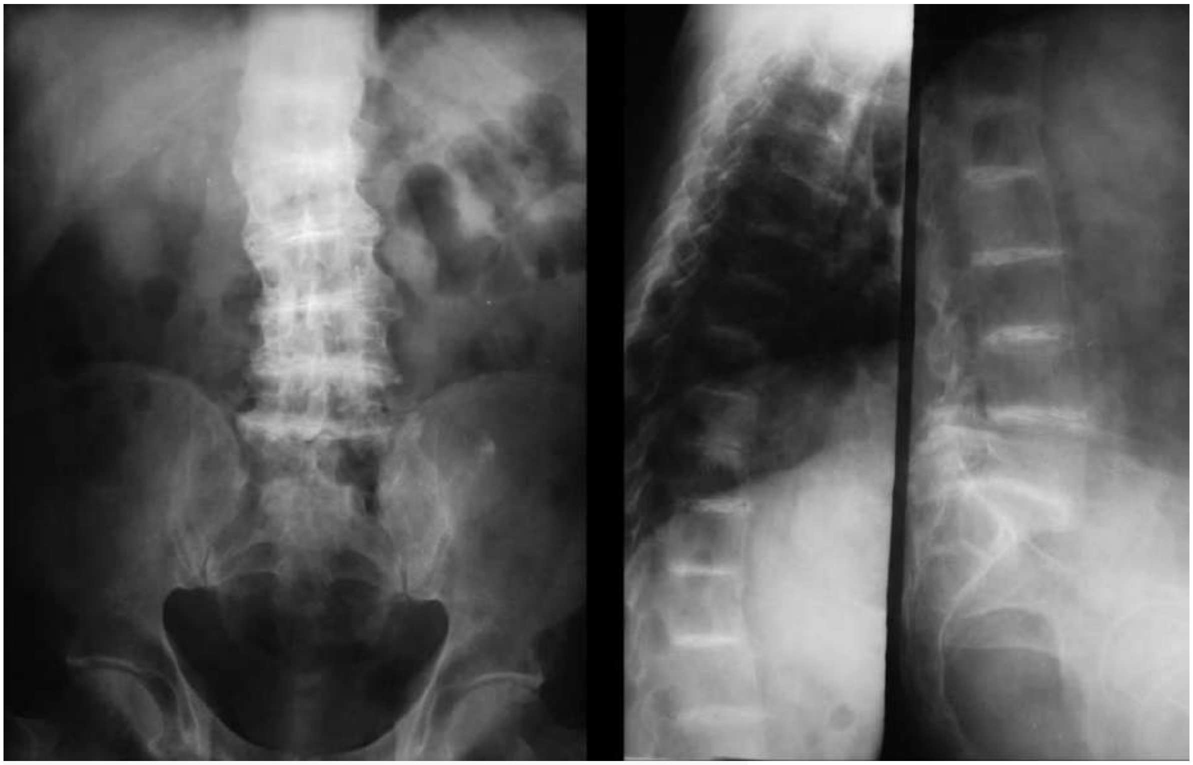
*secondary to phenylacetate, a phenylketone

## ALKAPTONURIA

Alkaptonuria (ochronosis) is a rare autosomal recessive disorder of phenylalanine and tyrosine metabolism caused by a lack of the enzyme homogentisic dioxygenase (HGD) which results in a build-up of toxic homogentisic acid. The kidneys filter the homogentisic acid (hence black urine) but eventually it accumulates in cartilage and other tissues.

Alkaptonuria is generally a benign and often asymptomatic condition. Possible features include:
- pigmented sclera
- urine turns black if left exposed to the air
- intervertebral disc calcification may result in back pain
- renal stones

Treatment
- high-dose vitamin C
- dietary restriction of phenylalanine and tyrosine



Multi-level intervertebral disc calcification with disc space narrowing

# ANDERSON-FABRY DISEASE

Overview
- X-linked recessive
- deficiency of alpha-galactosidase A

Features
- burning pain/paraesthesia in childhood
- angiokeratomas
- lens opacities
- proteinuria
- early cardiovascular disease

## X-LINKED DOMINANT

The following conditions are inherited in a X-linked dominant fashion*:

Alport's syndrome (in around 85% of cases - 10-15% of cases are inherited in an autosomal recessive fashion with rare autosomal dominant variants existing)
Rett syndrome
Vitamin D resistant rickets

*pseudohypoparathyroidism was previously classified as an X-linked dominant condition but has now been shown to be inherited in an autosomal dominant fashion in the majority of cases

## X-LINKED RECESSIVE

In X-linked recessive inheritance only males are affected. An exception to this seen in examinations are patients with Turner's syndrome, who are affected due to only having one X chromosome. X-linked recessive disorders are transmitted by heterozygote females (carriers) and male-to-male transmission is not seen. Affected males can only have unaffected sons and carrier daughters.

Each male child of a heterozygous female carrier has a 50% chance of being affected whilst each female child of a heterozygous female carrier has a 50% chance of being a carrier.

The possibility of an affected father having children with a heterozygous female carrier is generally speaking extremely rare. However, in certain Afro-Caribbean communities G6PD deficiency is relatively common and homozygous females with clinical manifestations of the enzyme defect are seen.

## X-LINKED RECESSIVE CONDITIONS

The following conditions are inherited in a X-linked recessive fashion:

Androgen insensitivity syndrome
Becker muscular dystrophy
Colour blindness
Duchenne muscular dystrophy
Fabry's disease
G6PD deficiency
Haemophilia A,B
Hunter's disease
Lesch-Nyhan syndrome
Nephrogenic diabetes insipidus

Ocular albinism
Retinitis pigmentosa
Wiskott-Aldrich syndrome

The following diseases have varying patterns of inheritance, with the majority being in an X-linked recessive fashion:

Chronic granulomatous disease (in > 70%)

# ALPHA-THALASSAEMIA

Alpha-thalassaemia is due to a deficiency of alpha chains in haemoglobin

Overview
- 2 separate alpha-globulin genes are located on each chromosome 16

Clinical severity depends on the number of alpha globulin alleles affected:
- If 1 or 2 alpha globulin alleles are affected then the blood picture would be hypochromic and microcytic, but the Hb level would be typically normal
- If are 3 alpha globulin alleles are affected results in a hypochromic microcytic anaemia with splenomegaly. This is known as Hb H disease
- If all 4 alpha globulin alleles are affected (i.e. homozygote) then death in utero (hydrops fetalis, Bart's hydrops)

# DISSEMINATED INTRAVASCULAR COAGULATION

Simultaneous coagulation and haemorrhage caused by the initial formation of thrombi which consume clotting factors (factors 5,8) and platelets, ultimately leading to bleeding.

Causes include:
- Infection
- Malignancy
- Trauma e.g. major surgery, burns, shock, dissecting aortic aneurysm
- Liver disease
- Obstetric complications

**Key points**
- Clinically bleeding is usually a dominant feature, bruising, ischaemia and organ failure
- Blood tests: prolonged clotting times, thrombocytopenia, decreased fibrinogen, increased fibrinogen degradation products
- Treat the underlying cause and supportive management

# CHILDHOOD SYNDROMES

Below is a list of common features of selected childhood syndromes

| Syndrome | Key features |
|---|---|
| Patau syndrome (trisomy 13) | Microcephalic, small eyes<br>Cleft lip/palate<br>Polydactyly<br>Scalp lesions |
| Edward's syndrome (trisomy 18) | Micrognathia<br>Low-set ears<br>Rocker bottom feet<br>Overlapping of fingers |
| Fragile X | Learning difficulties<br>Macrocephaly<br>Long face<br>Large ears<br>Macro-orchidism |
| Noonan syndrome | Webbed neck<br>Pectus excavatum<br>Short stature<br>Pulmonary stenosis |
| Pierre-Robin syndrome* | Micrognathia<br>Posterior displacement of the tongue (may result in upper airway obstruction)<br>Cleft palate |
| Prader-Willi syndrome | Hypotonia<br>Hypogonadism<br>Obesity |
| William's syndrome | Short stature<br>Learning difficulties<br>Friendly, extrovert personality<br>Transient neonatal hypercalcaemia<br>Supravalvular aortic stenosis |
| Cri du chat syndrome (chromosome 5p deletion syndrome) | Characteristic cry (hence the name) due to larynx and neurological problems<br>Feeding difficulties and poor weight gain<br>Learning difficulties<br>Microcephaly and micrognathism<br>Hypertelorism |

*this condition has many similarities with Treacher-Collins syndrome. One of the key differences is that Treacher-Collins syndrome is autosomal dominant so there is usually a family history of similar problems

# FRAGILE X SYNDROME

Fragile X syndrome is a trinucleotide repeat disorder.

Features in males
- learning difficulties
- large low set ears, long thin face, high arched palate
- macroorchidism
- hypotonia
- autism is more common
- mitral valve prolapse

Features in females (who have one fragile chromosome and one normal X chromosome) range from normal to mild

Diagnosis
- can be made antenatally by chorionic villus sampling or amniocentesis
- analysis of the number of CGG repeats using restriction endonuclease digestion and Southern blot analysis

# NOONAN SYNDROME

Often thought of as the 'male Turner's', Noonan syndrome is an autosomal dominant condition associated with a normal karyotype. It is thought to be caused by a defect in a gene on chromosome 12

As well as features similar to Turner's syndrome (webbed neck, widely-spaced nipples, short stature, pectus carinatum and excavatum), a number of characteristic clinical signs may also be seen:
- cardiac: pulmonary valve stenosis
- ptosis
- triangular-shaped face
- low-set ears
- coagulation problems: factor XI deficiency

# PRADER-WILLI SYNDROME

Prader-Willi syndrome is an example of genetic imprinting where the phenotype depends on whether the deletion occurs on a gene inherited from the mother or father:

- Prader-Willi syndrome if gene deleted from father
- Angelman syndrome if gene deleted from mother

Prader-Willi syndrome is associated with the absence of the active Prader-Willi gene on the long arm of chromosome 15. This may be due to:

- microdeletion of paternal 15q11-13 (70% of cases)
- maternal uniparental disomy of chromosome 15

Features

- hypotonia during infancy
- dysmorphic features
- short stature
- hypogonadism and infertility
- learning difficulties
- childhood obesity
- behavioural problems in adolescence

# WILLIAM'S SYNDROME

William's syndrome is an inherited neurodevelopmental disorder caused by a microdeletion on chromosome 7

Features

- elfin-like facies
- characteristic like affect - very friendly and social
- learning difficulties
- short stature
- transient neonatal hypercalcaemia
- supravalvular aortic stenosis

Diagnosis is made by FISH studies

# DIGEORGE SYNDROME

DiGeorge syndrome is a primary immunodeficiency disorder caused by T-cell deficiency and dysfunction. It is an example of a microdeletion syndrome (deletion of a section of chromosome 22).

It is also known as velocardiofacial syndrome and 22q11.2 deletion syndrome and is an autosomal dominant condition.

Features
- at risk of viral and fungal infections
- parathyroid gland hypoplasia → hypocalcaemic tetany
- thymus hypoplasia
- T-lymphocyte deficiency/dysfunction

It has a variable presentation however its features can be remembered with the mnemonic CATCH22:

- C - Cardiac abnormalities
- A - Abnormal facies
- T - Thymic aplasia
- C - Cleft palate
- H - Hypocalcaemia/ hypoparathyroidism
- 22 - Caused by chromosome 22 deletion

# MCCUNE-ALBRIGHT SYNDROME

McCune-Albright syndrome is not inherited, it is due to a random, somatic mutation in the GNAS gene.

Features
- precocious puberty
- cafe-au-lait spots
- polyostotic fibrous dysplasia
- short stature

# DOWN'S SYNDROME: EPIDEMIOLOGY AND GENETICS

Risk of Down's syndrome with increasing maternal age

| Age (years) | Risk |
|---|---|
| 20 | 1 in 1,500 |
| 30 | 1 in 800 |
| 35 | 1 in 270 |
| 40 | 1 in 100 |
| 45 | 1 in 50 or greater |

One way of remembering this is by starting at 1/1,000 at 30 years and then dividing the denominator by 3 (i.e. 3 times more common) for every extra 5 years of age

**Cytogenetics**

| Mode | % of cases | Risk of recurrence |
|---|---|---|
| Nondisjunction | 94% | 1 in 100 if under mother < 35 years |
| Robertsonian translocation (usually onto 14) | 5% | 10-15% if mother is translocation carrier<br>2.5% if father is translocation carrier |
| Mosaicism* | 1% | |

The chance of a further child with Down's syndrome is approximately 1 in 100 if the mother is less than 35 years old. If the trisomy 21 is a result of a translocation the risk is much higher

*Mosaicism is defined as the presence of two genetically different populations of cells in the body

# DOWN'S SYNDROME: FEATURES

Clinical features

- face: upslanting palpebral fissures, epicanthic folds, Brushfield spots in iris, protruding tongue, small low-set ears, round/flat face
- flat occiput
- single palmar crease, pronounced 'sandal gap' between big and first toe
- hypotonia
- congenital heart defects (40-50%, see below)
- duodenal atresia
- Hirschsprung's disease

Cardiac complications

- multiple cardiac problems may be present
- endocardial cushion defect (most common, 40%, also known as atrioventricular septal canal defects)
- ventricular septal defect (c. 30%)
- secundum atrial septal defect (c. 10%)
- tetralogy of Fallot (c. 5%)
- isolated patent ductus arteriosus (c. 5%)

Later complications

- subfertility: males are almost always infertile due to impaired spermatogenesis. Females are usually subfertile, and have an increased incidence of problems with pregnancy and labour
- learning difficulties
- short stature
- repeated respiratory infections (+hearing impairment from glue ear)
- acute lymphoblastic leukaemia
- hypothyroidism
- Alzheimer's disease
- atlantoaxial instability

## HIRSCHSPRUNG'S DISEASE

Hirschsprung's disease is caused by an aganglionic segment of bowel due to a developmental failure of the parasympathetic Auerbach and Meissner plexuses. Although rare (occurring in 1 in 5,000 births) it is an important differential diagnosis in childhood constipation

Possible presentations

- neonatal period e.g. failure or delay to pass meconium
- older children: constipation, abdominal distension

Associations

- 3 times more common in males
- Down's syndrome

# TRINUCLEOTIDE REPEAT DISORDERS

Trinucleotide repeat disorders are genetic conditions caused by an abnormal number of repeats (expansions) of a repetitive sequence of three nucleotides. These expansions are unstable and may enlarge which may lead to an earlier age of onset in successive generations - a phenomenon known as anticipation*. In most cases, an increase in the severity of symptoms is also noted

Examples - note dominance of neurological disorders

- Fragile X (CGG)
- Huntington's (CAG)
- myotonic dystrophy (CTG)
- Friedreich's ataxia* (GAA)
- spinocerebellar ataxia
- spinobulbar muscular atrophy
- dentatorubral pallidoluysian atrophy

*Friedreich's ataxia is unusual in not demonstrating anticipation

# INHERITED METABOLIC DISORDERS

### Glycogen storage disease

| Disorder | Deficient enzyme | Notes |
|---|---|---|
| Von Gierke's disease (type I) | Glucose-6-phosphatase | Hepatic glycogen accumulation. Key features include hypoglycaemia, lactic acidosis, hepatomegaly |
| Pompe's disease (type II) | Lysosomal alpha-1,4-glucosidase | Cardiac, hepatic and muscle glycogen accumulation. Key features include cardiomegaly |
| Cori disease (type III) | Alpha-1,6-glucosidase (debranching enzyme) | Hepatic, cardiac glycogen accumulation. Key features include muscle hypotonia |
| McArdle's disease (type V) | Glycogen phosphorylase (myophosphorylase) | Skeletal muscle glycogen accumulation. Key features include myalgia, myoglobinuria with exercise |

### Lysosomal storage disease

| Disorder | Defect | Notes |
|---|---|---|
| Gaucher's disease | Beta-glucocerebrosidase | Most common lipid storage disorder resulting in accumulation of glucocerebrosidase in the brain, liver and spleen. Key features include hepatosplenomegaly, aseptic necrosis of the femur |
| Tay-Sachs disease | Hexosaminidase A | Accumulation of $GM_2$ ganglioside within lysosomes. Key features include developmental delay, cherry red spot on the macula, liver and spleen normal size (*cf.* Niemann-Pick) |

| Disorder | Defect | Notes |
|---|---|---|
| Niemann-Pick disease | Sphingomyelinase | Key features include hepatosplenomegaly, cherry red spot on the macula |
| Fabry disease | Alpha-galactosidase-A | Accumulation of ceramide trihexoside. Key features include angiokeratomas, peripheral neuropathy of extemeties, renal failure |
| Krabbe's disease | Galactocerebrosidase | Key features include peripheral neuropathy, optic atrophy, globoid cells |
| Metachromatic leukodystrophy | Arylsulfatase A | Demyelination of the central and peripheral nervous system |

### Mucopolysaccharides

| Disorder | Defect | Notes |
|---|---|---|
| Hurler syndrome (type I) | Alpha-1-iduronidase | Accumulation of glycosaminoglycans (heparan and dermatan sulfate). Key features include gargoylism, hepatosplenomegaly, corneal clouding |
| Hunter syndrome (type II) | Iduronate sulfatase | Accumulation of glycosaminoglycans (heparan and dermatan sulfate). Key features include coarse facial features, behavioural problems/learning difficulties short stature, no corneal clouding |

# CONGENITAL HEART DISEASE: TYPES

Acyanotic - most common causes

- ventricular septal defects (VSD) - most common, accounts for 30%
- atrial septal defect (ASD)
- patent ductus arteriosus (PDA)
- coarctation of the aorta
- aortic valve stenosis

VSDs are more common than ASDs. However, in adult patients ASDs are the more common new diagnosis as they generally presents later.

Cyanotic - most common causes

- tetralogy of Fallot
- transposition of the great arteries (TGA)
- tricuspid atresia

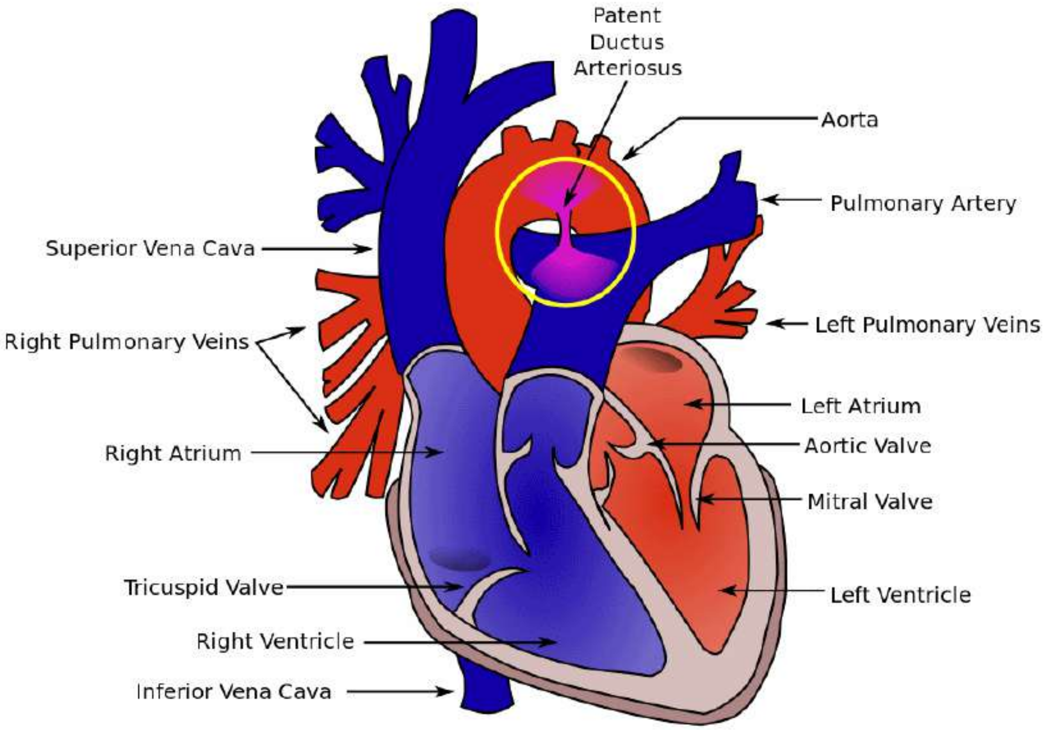
Fallot's is more common than TGA. However, at birth TGA is the more common lesion as patients with Fallot's generally presenting at around 1-2 months

The presence of cyanosis in pulmonary valve stenosis depends very much on the severity and any other coexistent defects.

# PATENT DUCTUS ARTERIOSUS

Overview

- a form of congenital heart defect
- generally classed as 'acyanotic'. However, uncorrected can eventually result in late cyanosis in the lower extremities, termed differential cynaosis.
- connection between the pulmonary trunk and descending aorta
- usually the ductus arteriosus closes with the first breaths due to increased pulmonary flow which enhances prostaglandins clearance
- more common in premature babies, born at high altitude or maternal rubella infection in the first trimester


Patent
Ductus
Arteriosus
Aorta
Pulmonary Artery
Superior Vena Cava
Left Pulmonary Veins
Right Pulmonary Veins
Left Atrium
Aortic Valve
Right Atrium
Mitral Valve
Left Ventricle
Tricuspid Valve
Right Ventricle
Inferior Vena Cava

Features

- left subclavicular thrill
- continuous 'machinery' murmur
- large volume, bounding, collapsing pulse
- wide pulse pressure
- heaving apex beat

Management

- indomethacin or ibupofen
    - given to the neonate
    - inhibits prostaglandin synthesis
    - closes the connection in the majority of cases
- if associated with another congenital heart defect amenable to surgery then prostaglandin E1 is useful to keep the duct open until after surgical repair

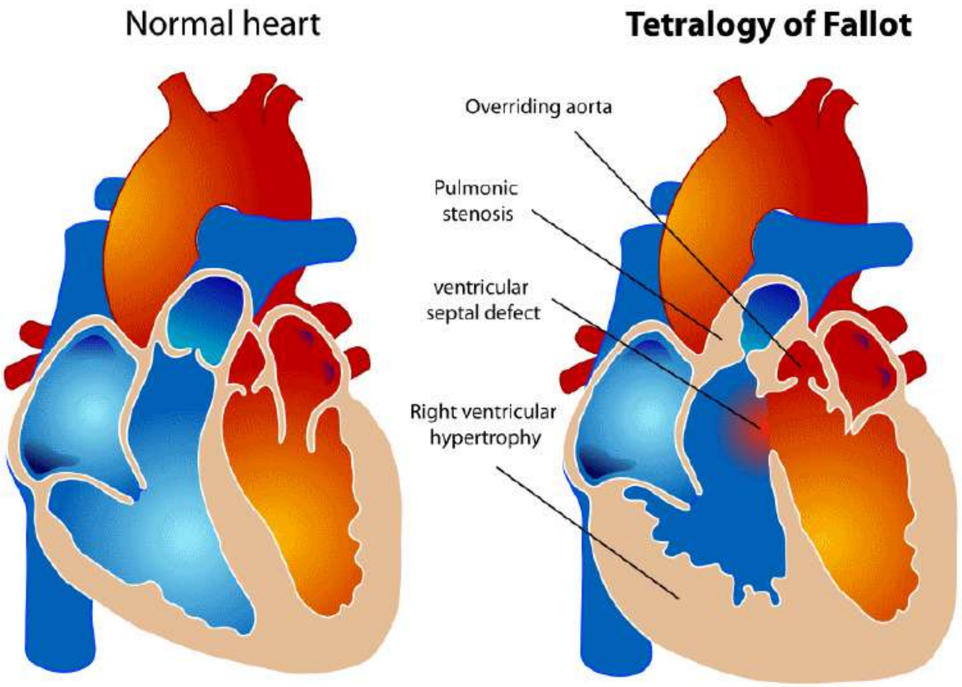
## TETRALOGY OF FALLOT

Tetralogy of Fallot (TOF) is the most common cause of cyanotic congenital heart disease*. It typically presents at around 1-2 months, although may not be picked up until the baby is 6 months old

TOF is a result of anterior malalignment of the aorticopulmonary septum. The four characteristic features are:

- ventricular septal defect (VSD)

- right ventricular hypertrophy
- right ventricular outflow tract obstruction, pulmonary stenosis
- overriding aorta


Normal heart
Tetralogy of Fallot
Overriding aorta
Pulmonic stenosis
ventricular septal defect
Right ventricular hypertrophy

The severity of the right ventricular outflow tract obstruction determines the degree of cyanosis and clinical severity

Other features

- cyanosis
- causes a right-to-left shunt
- ejection systolic murmur due to pulmonary stenosis (the VSD doesn't usually cause a murmur)
- a right-sided aortic arch is seen in 25% of patients
- chest x-ray shows a 'boot-shaped' heart, ECG shows right ventricular hypertrophy

Management

- surgical repair is often undertaken in two parts
- cyanotic episodes may be helped by beta-blockers to reduce infundibular spasm

*however, at birth transposition of the great arteries is the more common lesion as patients with TOF generally present at around 1-2 months

# TRANSPOSITION OF THE GREAT ARTERIES

Transposition of the great arteries (TGA) is a form of cyanotic congenital heart disease. It is caused by the failure of the aorticopulmonary septum to spiral during septation. Children of diabetic mothers are at an increased risk of TGA.

Basic anatomical changes
- aorta leaves the right ventricle
- pulmonary trunk leaves the left ventricle

Clinical features
- cyanosis
- tachypnoea
- loud single S2
- prominent right ventricular impulse
- 'egg-on-side' appearance on chest x-ray

Management
- maintenance of the ductus arteriosus with prostaglandins
- surgical correction is the definite treatment.

# EBSTEIN'S ANOMALY

Ebstein's anomaly is a congenital heart defect characterised by low insertion of the tricuspid valve resulting in a large atrium and small ventricle. It is sometimes referred to as 'atrialisation' of the right ventricle.

Associations
- tricuspid incompetence (pan-systolic murmur, giant V waves in JVP)
- Wolff-Parkinson White syndrome

Ebstein's anomaly may be caused by exposure to lithium in-utero

# ATHEROSCLEROSIS

Atherosclerosis is a complex process which develops over a number of years. A number of changes can be seen:

- initial endothelial dysfunction is triggered by a number of factors such as smoking, hypertension and hyperglycaemia
- this results in a number of changes to the endothelium including pro-inflammatory, pro-oxidant, proliferative and reduced nitric oxide bioavailability
- fatty infiltration of the subendothelial space by low-density lipoprotein (LDL) particles
- monocytes migrate from the blood and differentiate into macrophages. These macrophages then phagocytose oxidized LDL, slowly turning into large 'foam cells'. As these macrophages die the result can further propagate the inflammatory process.
- smooth muscle proliferation and migration from the tunica media into the intima results in formation of a fibrous capsule covering the fatty plaque.

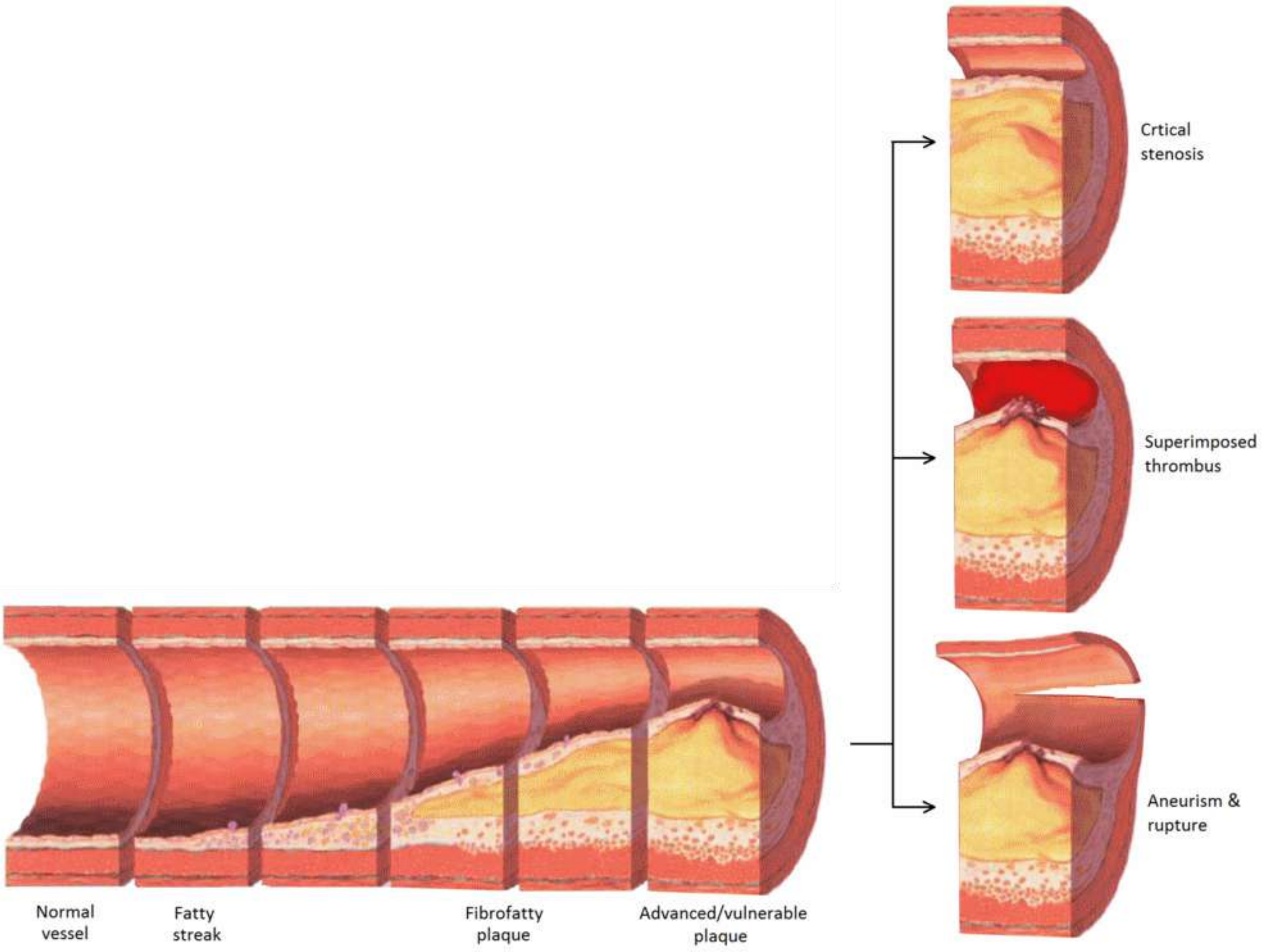
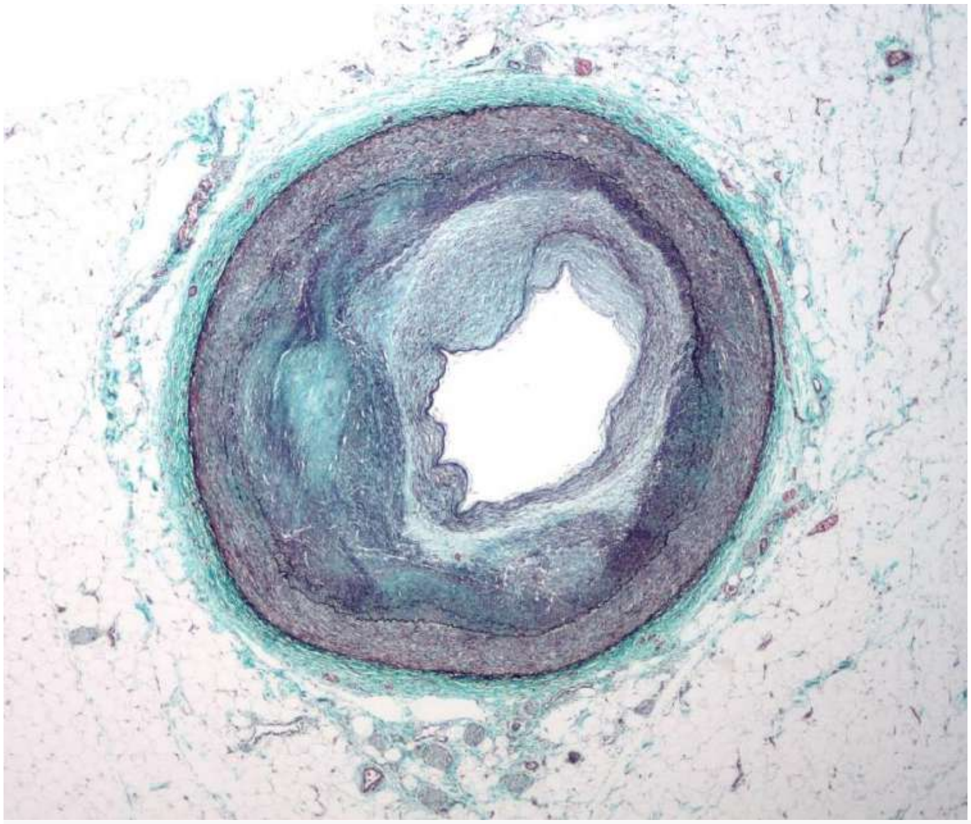

Crtical
stenosis
Superimposed
thrombus
Aneurism &
rupture
Normal
vessel
Fatty
streak
Fibrofatty
plaque
Advanced/vulnerable
plaque

Diagram showing the progression of atherosclerosis in the coronary arteries with associated complications on the right.

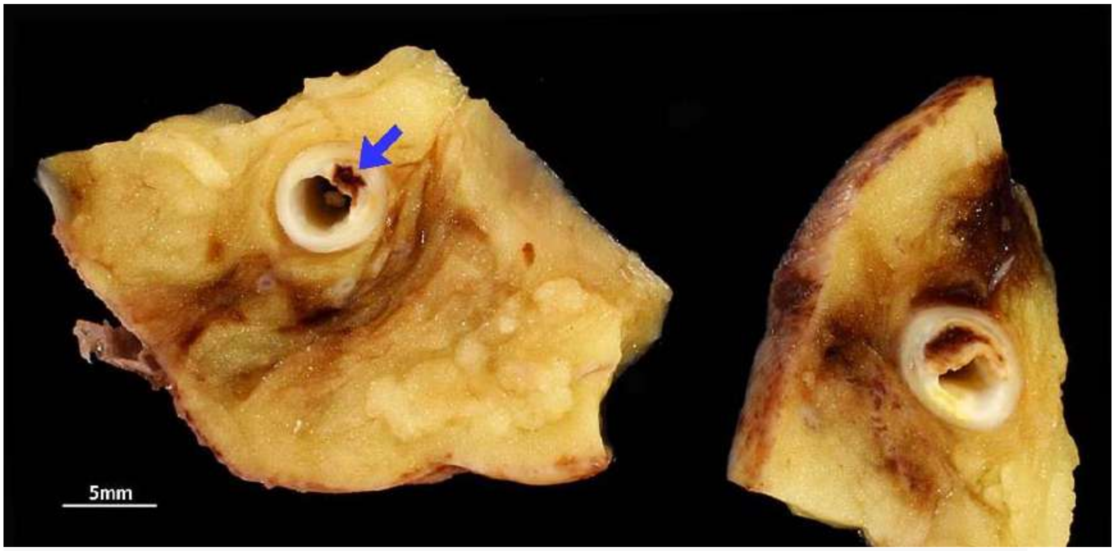


Slide showing a markedly narrowed coronary artery secondary to atherosclerosis. Stained with Masson's trichrome.

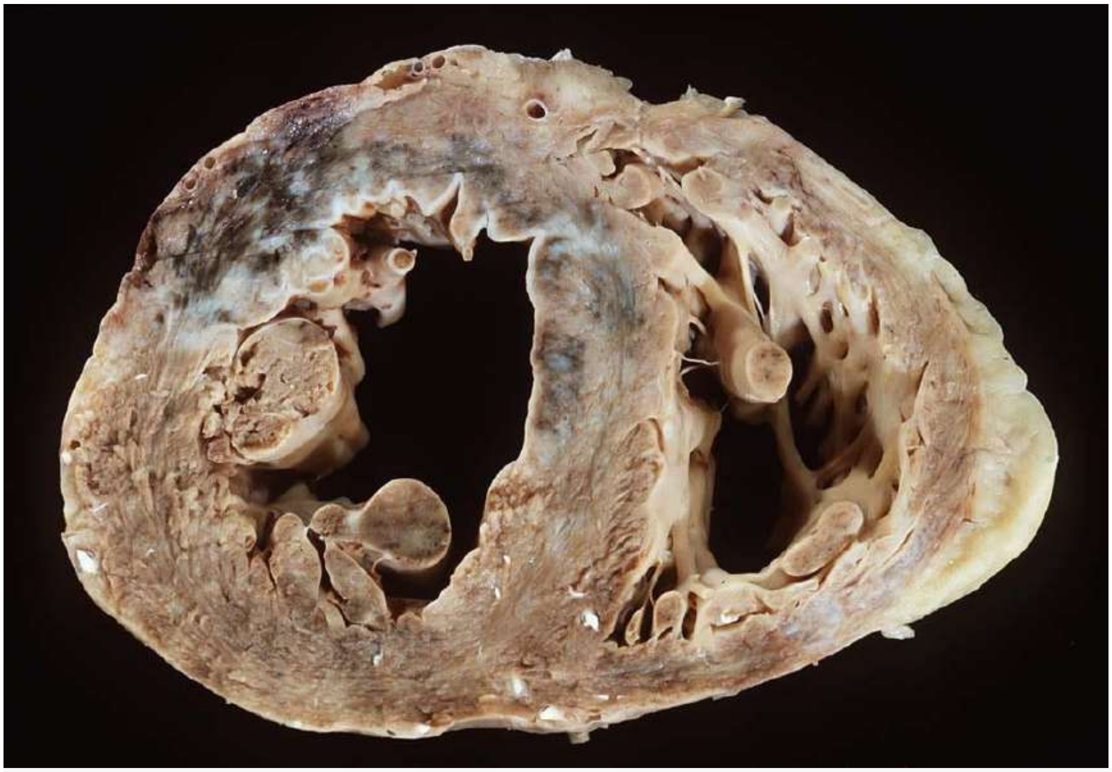
**Complications of atherosclerosis**

Taking the coronary arteries as an example, once a plaque has formed a number of complications can develop:

- the plaque forms a physical blockage in the lumen of the coronary artery. This may cause reduced blood flow and hence oxygen to the myocardium, particularly at times of increased demand, resulting clinically in angina
- the plaque may rupture, potentially causing a complete occlusion of the coronary artery. This may result in a myocardial infarction



Ruptured coronary artery plaque resulting in thrombosis and associated myocardial infarction.



Pathological specimen showing infarction of the anteroseptal and lateral wall of the left ventricle. There is a background of biventricular myocardial hypertrophy.

## HYPERLIPIDAEMIA: SECONDARY CAUSES

Causes of predominantly hypertriglyceridaemia

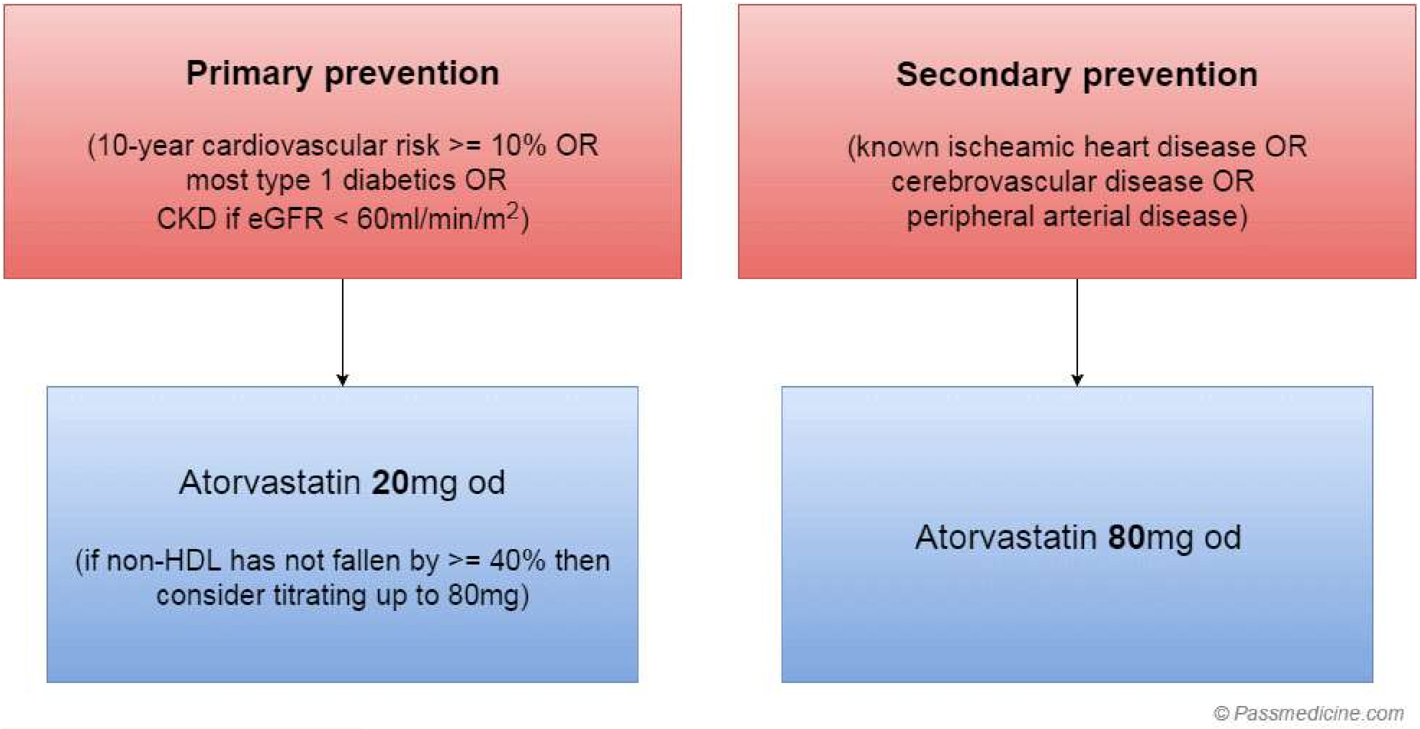
- diabetes mellitus (types 1 and 2)
- obesity
- alcohol
- chronic renal failure
- drugs: thiazides, non-selective beta-blockers, unopposed oestrogen
- liver disease

Causes of predominantly hypercholesterolaemia

- nephrotic syndrome
- cholestasis
- hypothyroidism

# HYPERLIPIDAEMIA: MANAGEMENT

In 2014 NICE updated their guidelines on lipid modification. This proved highly controversial as it meant that we should be recommending statins to a significant proportion of the population over the age of 60 years. Anyway, the key points of the new guidelines are summarised below.



Primary prevention
(10-year cardiovascular risk >= 10% OR
most type 1 diabetics OR
CKD if eGFR < 60ml/min/$m^2$)
Secondary prevention
(known ischeamic heart disease OR
cerebrovascular disease OR
peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then
consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

**Primary prevention - who and how to assess risk**

A systematic strategy should be used to identify people aged over 40 years who are likely to be at high risk of cardiovascular disease (CVD), defined as a 10-year risk of **10%** or greater.

NICE recommend we use the **QRISK2** CVD risk assessment tool for patients aged <= 84 years. Patients >= 85 years are at high risk of CVD due to their age. QRISK2 should not be used in the following situations as there are more specific guidelines for these patient groups:

- type 1 diabetics
- patients with an estimated glomerular filtration rate (eGFR) less than 60 ml/min and/or albuminuria
- patients with a history of familial hyperlipidaemia

NICE suggest QRISK2 may underestimate CVD risk in the following population groups:

- people treated for HIV
- people with serious mental health problems
- people taking medicines that can cause dyslipidaemia such as antipsychotics, corticosteroids or immunosuppressant drugs

- people with autoimmune disorders/systemic inflammatory disorders such as systemic lupus erythematosus

**Measuring lipid levels**

When measuring lipids both the total cholesterol and HDL should be checking to provide the most accurate risk of CVD. A full lipid profile should also be checked (i.e. including triglycerides) before starting a statin. The samples does not need to be fasting.

In the vast majority of patient the cholesterol measurements will be fed into the QRISK2 tool. If however the patient's cholesterol is very high we should consider familial hyperlipidaemia. NICE recommend the following that we should consider the possibility of familial hypercholesterolaemia and investigate further if the total cholesterol concentration is > 7.5 mmol/l and there is a family history of premature coronary heart disease. They also recommend referring people with a total cholesterol > 9.0 mmol/l or a non-HDL cholesterol (i.e. LDL) of > 7.5 mmol/l even in the absence of a first-degree family history of premature coronary heart disease.

**Interpreting the QRISK2 result**

Probably the headline changes in the 2014 guidelines was the new, lower cut-off of 10-year CVD risk cut-off of 10%.

**NICE now recommend we offer a statin to people with a QRISK2 10-year risk of >= 10%**

Lifestyle factors are of course important and NICE recommend that we give patients the option of having their CVD risk reassessed after a period of time before starting a statin.

Atorvastatin 20mg should be offered first-line.

**Special situations**

Type 1 diabetes mellitus

- NICE recommend that we 'consider statin treatment for the primary prevention of CVD in all adults with type 1 diabetes'
- atorvastatin 20 mg should be offered if type 1 diabetics who are:
- → older than 40 years, or
- → have had diabetes for more than 10 years or
- → have established nephropathy or
- → have other CVD risk factors

Chronic kidney disease (CKD)

- atorvastatin 20mg should be offered to patients with CKD

- increase the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and the eGFR > 30 ml/min. If the eGFR is < 30 ml/min a renal specialist should be consulted before increasing the dose

**Secondary prevention**

All patients with CVD should be taking a statin in the absence of any contraindication.

Atorvastatin 80mg should be offered first-line.

**Follow-up of people started on statins**

NICE recommend we follow-up patients at 3 months
- repeat a full lipid profile
- if the non-HDL cholesterol has not fallen by at least 40% concordance and lifestyle changes should be discussed with the patient
- NICE recommend we consider increasing the dose of atorvastatin up to 80mg

**Lifestyle modifications**

These are in many ways predictable but NICE make a number of specific points:

Cardioprotective diet
- total fat intake should be <= 30% of total energy intake
- saturated fats should be <= 7% of total energy intake
- intake of dietary cholesterol should be < 300 mg/day
- saturated fats should be replaced by monounsaturated and polyunsaturated fats where possible
- replace saturated and monounsaturated fat intake with olive oil, rapeseed oil or spreads based on these oils
- choose wholegrain varieties of starchy food
- reduce their intake of sugar and food products containing refined sugars including fructose
- eat at least 5 portions of fruit and vegetables per day
- eat at least 2 portions of fish per week, including a portion of oily fish
- eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week

Physical activity
- each week aim for at least 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity aerobic activity or a mix of moderate and vigorous aerobic activity
- do musclestrengthening activities on 2 or more days a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms) in line with national guidance for the general population

Weight management

- no specific advice is given, overweight patients should be managed in keeping with relevant NICE guidance

Alcohol intake

- again no specific advice, other than the general recommendation that males drink no more than 3-4 units/day and females no more than 2-3 units/day

Smoking cessation

- smokers should be encouraged to quit

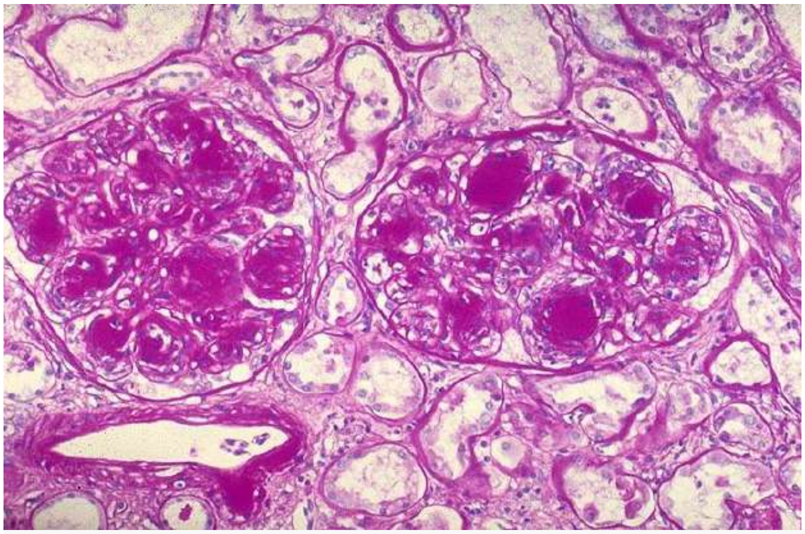
# DIABETIC NEPHROPATHY

Basics

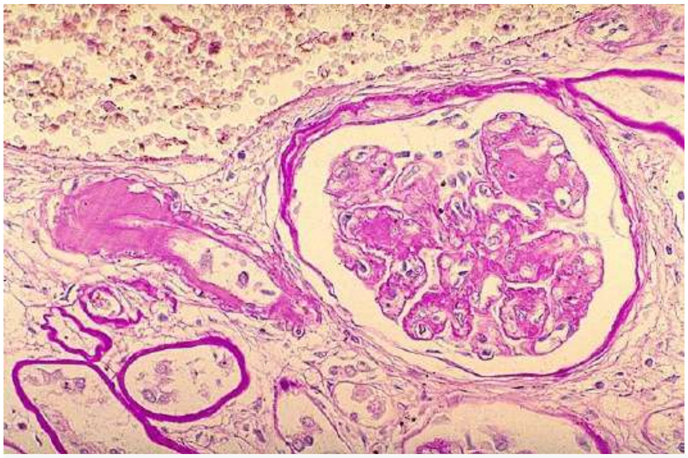
- commonest cause of end-stage renal disease (ESRD) in the western world
- 33% of patients with type 1 diabetes mellitus have diabetic nephropathy by the age of 40 years
- approximately 5-10% of patients with type 1 diabetes mellitus develop (ESRD)

The pathophysiology is poorly understood, however:

- changes to the haemodynamics of the glomerulus is thought to be key, which leads to an increased glomerular capillary pressure
- non-enzymatic glycosylation of the basement membrane is thought to play a key role
- histological changes include: basement membrane thickening, capillary obliteration, mesangial widening. Nodulular hyaline areas develop in the glomuli - Kimmelstiel-Wilson nodules



Thickening of the basement membrane is seen alongside multiple Kimmelstiel-Wilson nodules



Severe arteriolosclerosis is seen in the afferent arteriole on the left of the slide. Multiple, smaller acellular nodules are seen in the glomerulus - Kimmelstiel-Wilson nodules. The tubular basement membrane is also thickened

## Risk factors for developing diabetic nephropathy

| Modifiable | Non-modifiable |
|---|---|
| Hypertension<br>Hyperlipidaemia<br>Smoking<br>Poor glycaemic control<br>Raised dietary protein | Male sex<br>Duration of diabetes<br>Genetic predisposition (e.g. ACE gene polymorphisms) |

# MUCORMYCOSIS

Mucormycosis is a fungal infection that is more commonly seen in poorly controlled diabetes. It typically infects the sinuses, lungs and brain.

# URINARY CASTS

The table below lists the most common causes of the different types of urinary cast:

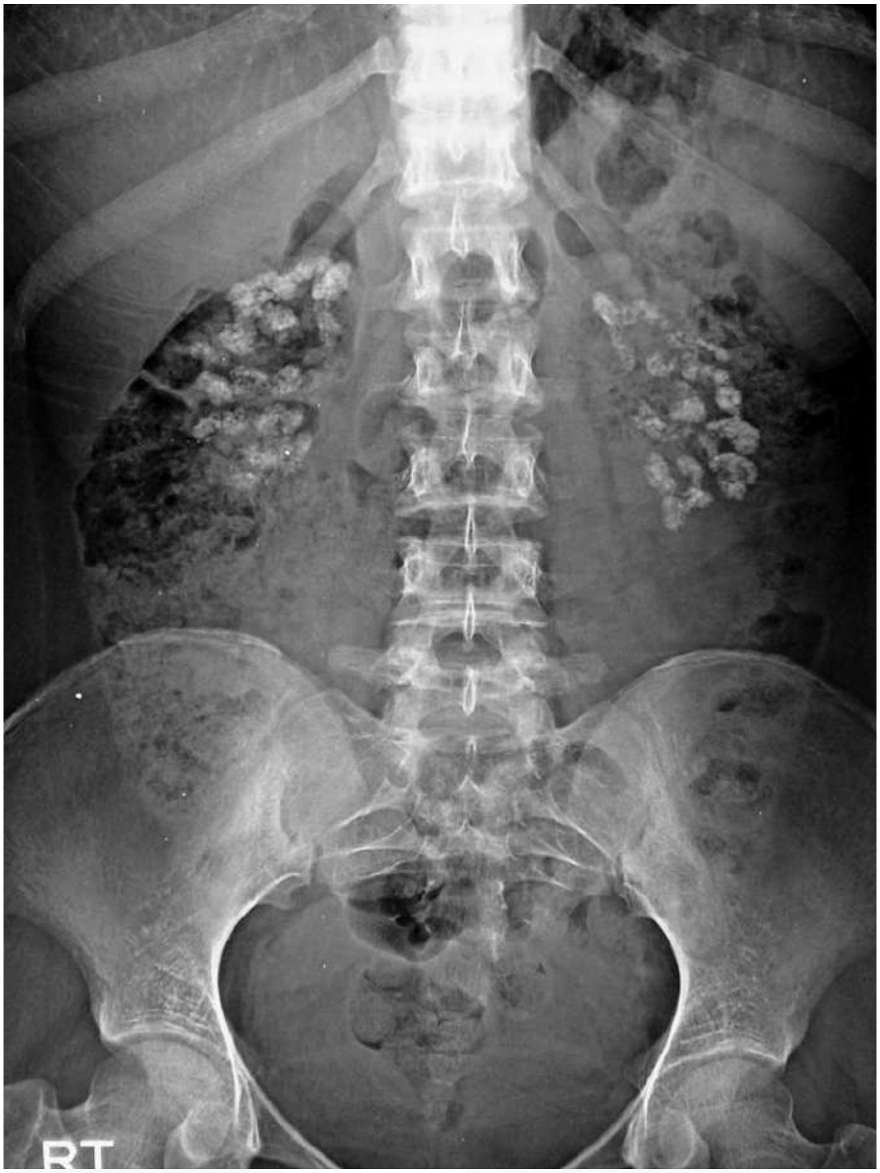
| Type of cast | Associated conditions |
|---|---|
| Red blood cell casts | Glomerulonephritis<br>Renal ischaemia and infarction |
| White blood cell casts | Acute pyelonephritis<br>Interstitial nephritis |
| Granular ('muddy-brown') casts | Acute tubular necrosis |
| Hyaline casts | Common and non-specific<br>May be seen following exercise or dehydration |
| Epithelial casts | Acute tubular necrosis |
| Waxy casts | Advanced chronic kidney disease |
| Fatty casts | Nephrotic syndrome |

# RENAL TUBULAR ACIDOSIS

All three types of renal tubular acidosis (RTA) are associated with hyperchloraemic metabolic acidosis (normal anion gap).

Type 1 RTA (distal)

- inability to generate acid urine (secrete H+) in distal tubule
- causes hypokalaemia
- complications include nephrocalcinosis and renal stones
- causes include idiopathic, rheumatoid arthritis, SLE, Sjogren's, amphotericin B toxicity, analgesic nephropathy



Abdominal x-ray showing nephrocalcinosis - a classical finding in type 1 RTA

Type 2 RTA (proximal)

- decreased HCO3- reabsorption in proximal tubule

- causes hypokalaemia
- complications include osteomalacia
- causes include idiopathic, as part of Fanconi syndrome, Wilson's disease, cystinosis, outdated tetracyclines, carbonic anhydrase inhibitors (acetazolamide, topiramate)

Type 4 RTA (hyperkalaemic)

- reduction in aldosterone leads in turn to a reduction in proximal tubular ammonium excretion
- causes hyperkalaemia
- causes include hypoaldosteronism, diabetes

# RENAL STONES

| Type of stones | Features | Percentage of all calculi |
|---|---|---|
| Calcium oxalate | Hypercalciuria is a major risk factor (various causes)<br>Hyperoxaluria may also increase risk<br>Hypocitraturia increases risk because citrate forms complexes with calcium making it more soluble<br>Stones are radio-opaque (though less than calcium phosphate stones)<br>Hyperuricosuria may cause uric acid stones to which calcium oxalate binds | 85% |
| Cystine | Inherited recessive disorder of transmembrane cystine transport leading to decreased absorption of cystine from intestine and renal tubule<br>Multiple stones may form<br>Relatively radiodense because they contain sulphur | 1% |
| Uric acid | Uric acid is a product of purine metabolism<br>May precipitate when urinary pH low<br>May be caused by diseases with extensive tissue breakdown e.g. malignancy<br>More common in children with inborn errors of metabolism<br>Radiolucent | 5-10% |
| Calcium phosphate | May occur in renal tubular acidosis, high urinary pH increases supersaturation of urine with calcium and phosphate<br>Renal tubular acidosis types 1 and 3 increase risk of stone formation (types 2 and 4 do not)<br>Radio-opaque stones (composition similar to bone) | 10% |
| Struvite | Stones formed from magnesium, ammonium and phosphate<br>Occur as a result of urease producing bacteria (and are thus associated with chronic infections)<br>Under the alkaline conditions produced, the crystals can precipitate<br>Slightly radio-opaque | 2-20% |

**Effect of urinary pH on stone formation**

Urine pH will show individual variation (from pH 5-7). Post prandially the pH falls as purine metabolism will produce uric acid. Then the urine becomes more alkaline (alkaline tide). When the stone is not available for analysis the pH of urine may help to determine which stone was present.

| Stone type | Urine acidity | Mean urine pH |
|---|---|---|
| Calcium phosphate | Normal- alkaline | >5.5 |
| Calcium oxalate | Variable | 6 |
| Uric acid | Acid | 5.5 |
| Struvate | Alkaline | >7.2 |
| Cystine | Normal | 6.5 |

# EXOTOXINS AND ENDOTOXINS

Exotoxins are secreted by bacteria where as endotoxins are only released following lysis of the cell. Exotoxins are generally released by Gram positive bacteria with the notable exceptions of Vibrio cholerae and some strains of E. coli

It is possible to classify exotoxins by their primary effects:

- pyrogenic toxins
- enterotoxins
- neurotoxins
- tissue invasive toxins
- miscellaneous toxins

**Pyrogenic toxins**

Pyrogenic toxins stimulate the release of endogenous cytokines resulting in fever, rash etc. They are superantigens which bridge the MHC class II protein on antigen-presenting cells with the T cell receptor on the surface of T cells resulting in massive cytokine release.

| Organism | Toxin | Notes |
|---|---|---|
| *Staphylococcus aureus* | Toxic shock syndrome (TSST-1 superantigen) toxin | Results in high fever, hypotension, exfoliative rash |
| *Streptococcus pyogenes* | Streptococcal pyrogenic exotoxin A & C | Results in scarlet fever |

**Enterotoxins**

Enterotoxins act on the gastrointestinal tract causing one of two patterns of illness:

- diarrhoeal illness
- vomiting illness ('food poisoning')

| Organism | Toxin | Notes |
|---|---|---|
| *Vibrio cholerae* | Cholera toxin | Causes activation of adenylate cyclase (via $G_s$) leading to increases in cAMP levels, which in turn leads to increased chloride secretion and reduced sodium absorption |
| *Shigella dysenteriae* | Shiga toxin | Inactivates 60S ribosome → epithelial cell death |
| *Escherichia coli* | 1. Heat labile toxin<br>2. Heat stabile toxin | 1. Activates adenylate cyclase (via $G_s$), increasing cAMP → watery diarrhoea<br>2. Activates guanylate cyclase, increasing cGMP → watery diarrhoea |
| *Staphylococcus aureus* | *Staphylococcus aureus* enterotoxin | Vomiting and diarrhoeal illness lasting < 24 hours |
| *Bacillus cereus* | Cereulide | Potent cytotoxin that destroys mitochondria. Causes a vomiting illness which may present within 4 hours of ingestion |

### Neurotoxins

Neurotoxins act on the nerves (tetanus) or the neuromuscular junction (botulism) causing paralysis.

| Organism | Toxin | Notes |
|---|---|---|
| *Clostridium tetani* | Tetanospasmin | Blocks the release of the inhibitory neurotransmitters GABA and glycine resulting in continuous motor neuron activity → continuous muscle contraction → lockjaw and respiratory paralysis |
| *Clostridium botulinum* | Botulinum toxin | Blocks acetylcholine (ACh) release leading to flaccid paralysis |

### Tissue invasive toxins

| Organism | Toxin | Notes |
|---|---|---|
| *Clostridium perfringens* | α-toxin, a lecithinase | Causes gas gangrene (myonecrosis) and haemolysis |
| *Staphylococcus aureus* | Exfoliatin | Staphylococcal scalded skin syndrome |

### Miscellaneous toxins

| Organism | Toxin | Notes |
|---|---|---|
| *Corynebacterium diphtheriae* | Diphtheria toxin | ADP ribosylates elogation factor (EF-2), resulting in inhibition, causing a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Systemic distribution may produce necrosis of myocardial, neural and renal tissue |
| *Pseudomonas aeruginosa* | Exotoxin A | Also inhibits EF-2 by the same mechanism as above |
| *Bacillus anthracis* | Oedema factor (EF) | Forms a calmodulin-dependent adenylate cyclase which increases cAMP, impairing the function of neutrophils/macrophages → reduced phagocytosis |
| *Bordetella pertussis* | Pertussis exotoxin | Inhibits $G_i$ leading to increases in cAMP levels, impairing the function of neutrophils/macrophages → reduced phagocytosis |

### Endotoxins

Endotoxins are lipopolysaccharides that are released from Gram-negative bacteria such as Neisseria meningitidis.

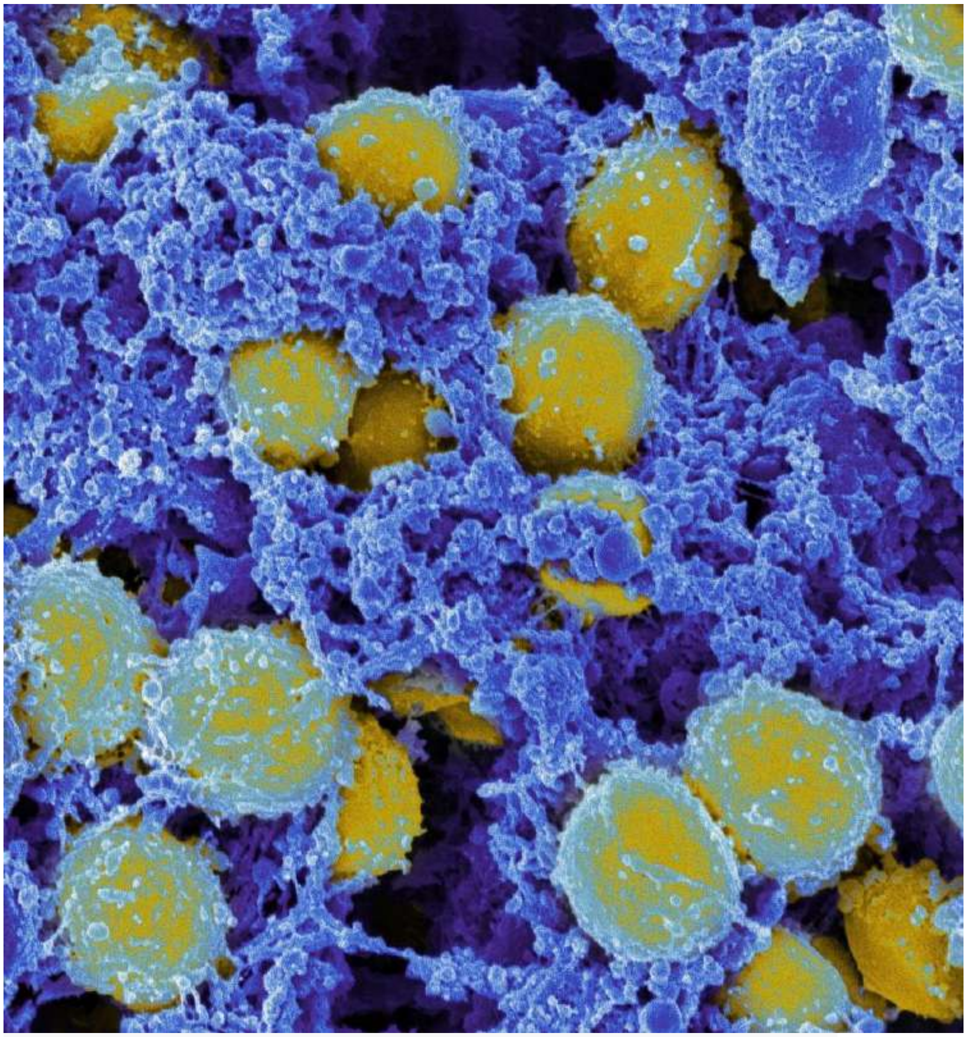
# STAPHYLOCOCCI

Staphylococci are a common type of bacteria which are often found normal commensal organisms but may also cause invasive disease. Some basic facts include:

- Gram-positive cocci
- facultative anaerobes
- produce catalase

The two main types of Staphylococci you need to know about are Staphylococcus aureus and Staphylococcus epidermidis.

| ***Staphylococcus aureus*** | ***Staphylococcus epidermidis*** |
|---|---|
| • Coagulase-positive<br>• Causes skin infections (e.g. cellulitis), abscesses, osteomyelitis, toxic shock syndrome | • Coagulase-negative<br>• Cause of central line infections and infective endocarditis |



Scanning electromicrograph of Staphylococcus aureus bacteria. Credit: NIAID

# ESCHERICHIA COLI

Escherichia coli is a facultative anaerobic, lactose-fermenting, Gram negative rod which is a normal gut commensal.

E. coli infections lead to a variety of diseases in humans including:

- diarrhoeal illnesses
- UTIs

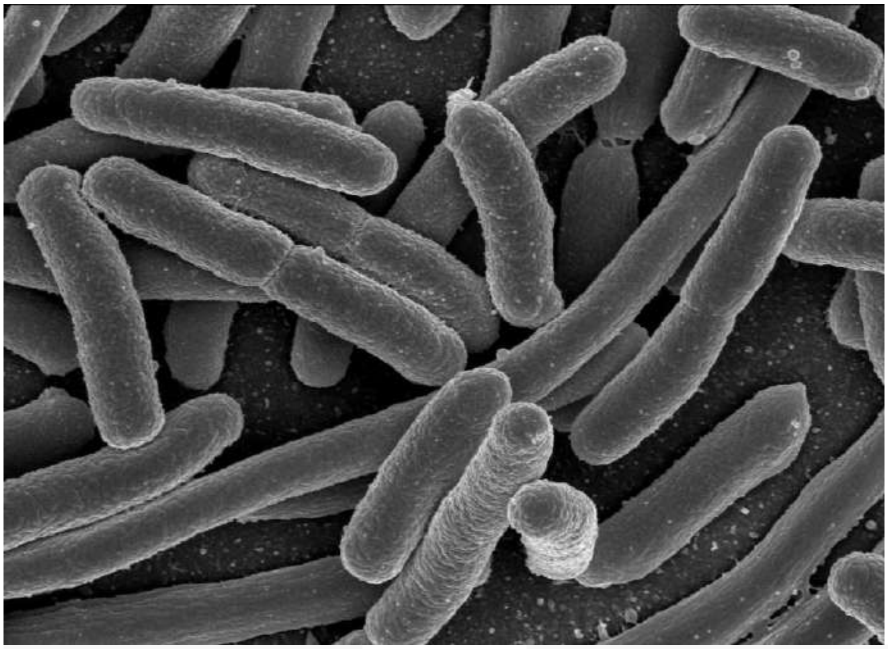
- neonatal meningitis

Serotypes

E. coli may be classified according to the antigens which may trigger an immune response:

| Antigen | Origin | Notes |
|---|---|---|
| O | Lipopolysaccharide layer | |
| K | Capsule | Neonatal meningitis secondary to E. coli is usually caused by a serotype that contains the capsular antigen K-1 |
| H | Flagellin | |

E. coli O157:H7 is a particular strain associated with severe, haemorrhagic, watery diarrhoea. It has a high mortality rate and can be complicated by haemolytic uraemic syndrome. It is often spread by contaminated ground beef.



Scanning electron micrograph of *Escherichia coli*, grown in culture and adhered to a cover slip. Credit: NIAID

# CAMPYLOBACTER

Campylobacter is the commonest bacterial cause of infectious intestinal disease in the UK. The majority of cases are caused by the Gram-negative bacillus Campylobacter jejuni. It is spread by the faecal-oral route and has an incubation period of 1-6 days.

Features

- prodrome: headache malaise

- diarrhoea: often bloody
- abdominal pain: may mimic appendicitis

Management
- usually self-limiting
- the BNF advises treatment if severe or the patient is immunocompromised. Clinical Knowledge summaries also recommend antibiotics if severe symptoms (high fever, bloody diarrhoea, or more than eight stools per day) or symptoms have last more than one week
- the first-line antibiotic is clarithromycin
- ciprofloxacin is an alternative although the BNF states that 'Strains with decreased sensitivity to ciprofloxacin isolated frequently'

Complications
- Guillain-Barre syndrome may follow Campylobacter jejuni infections
- Reiter's syndrome
- septicaemia, endocarditis, arthritis

# MYCOBACTERIUM MARINUM

Mycobacterium marinum is one of many mycobacteria that can cause disease in humans. Fish tank granuloma typically presents in patients who have had an exposure to, or frequently work with fish. It has an incubation period of 3-4 weeks and lesions can be painful or painless. A cut or break in the skin can be enough for the organism to enter the blood stream and track up the lymphatic system (sporotrichoid spread). Treatment options include tetracyclines, fluoroquinolones, sulfonamides and macrolides.

# CONGENITAL INFECTIONS

The major congenital infections encountered in examinations are rubella, toxoplasmosis and cytomegalovirus

Cytomegalovirus is the most common congenital infection in the UK. Maternal infection is usually asymptomatic

| | Rubella | Toxoplasmosis | Cytomegalovirus |
|---|---|---|---|
| **Characteristic features** | Sensorineural deafness<br>Congenital cataracts<br>Congenital heart disease (e.g. patent ductus arteriosus)<br>Glaucoma | Cerebral calcification<br>Chorioretinitis<br>Hydrocephalus | Growth retardation<br>Purpuric skin lesions |
| **Other features** | Growth retardation<br>Hepatosplenomegaly<br>Purpuric skin lesions<br>'Salt and pepper' chorioretinitis<br>Microphthalmia<br>Cerebral palsy | Anaemia<br>Hepatosplenomegaly<br>Cerebral palsy | Sensorineural deafness<br>Encephalitis/seizures<br>Pneumonitis<br>Hepatosplenomegaly<br>Anaemia<br>Jaundice<br>Cerebral palsy |

# CHILDHOOD INFECTIONS

The table below summarises the main characteristics of childhood infections

| Infection | Features |
|---|---|
| **Chickenpox** | Fever initially<br>Itchy, rash starting on head/trunk before spreading. Initially macular then papular then vesicular<br>Systemic upset is usually mild |
| **Measles** | Prodrome: irritable, conjunctivitis, fever<br>Koplik spots: white spots ('grain of salt') on buccal mucosa<br>Rash: starts behind ears then to whole body, discrete maculopapular rash becoming blotchy & confluent |
| **Mumps** | Fever, malaise, muscular pain<br>Parotitis ('earache', 'pain on eating'): unilateral initially then becomes bilateral in 70% |
| **Rubella** | Rash: pink maculopapular, initially on face before spreading to whole body, usually fades by the 3-5 day<br>Lymphadenopathy: suboccipital and postauricular |
| **Erythema infectiosum** | Also known as fifth disease or 'slapped-cheek syndrome'<br>Caused by parvovirus B19 |

| Infection | Features |
|---|---|
|  | Lethargy, fever, headache<br>'Slapped-cheek' rash spreading to proximal arms and extensor surfaces |
| **Scarlet fever** | Reaction to erythrogenic toxins produced by Group A haemolytic streptococci<br>Fever, malaise, tonsillitis<br>'Strawberry' tongue<br>Rash - fine punctate erythema sparing the area around the mouth (circumoral pallor) |
| **Hand, foot and mouth disease** | Caused by the coxsackie A16 virus<br>Mild systemic upset: sore throat, fever<br>Vesicles in the mouth and on the palms and soles of the feet |

# DIARRHOEA IN CHILDREN

Gastroenteritis
- main risk is severe dehydration
- most common cause is rotavirus - typically accompanied by fever and vomiting for the first 2 days. The diarrhoea may last up to a week
- treatment is rehydration

**Chronic diarrhoea**
Infants
- most common cause in the developed world is cows' milk intolerance
- toddler diarrhoea: stools vary in consistency, often contain undigested food
- coeliac disease
- post-gastroenteritis lactose intolerance

# CHICKENPOX

Chickenpox is caused by primary infection with varicella zoster virus. Shingles is a reactivation of the dormant virus in dorsal root ganglion

Chickenpox is highly infectious
- spread via the respiratory route
- can be caught from someone with shingles
- infectivity = 4 days before rash, until 5 days after the rash first appeared*
- incubation period = 10-21 days

Clinical features (tend to be more severe in older children/adults)
- fever initially
- itchy, rash starting on head/trunk before spreading. Initially macular then papular then vesicular

- systemic upset is usually mild

Management is supportive

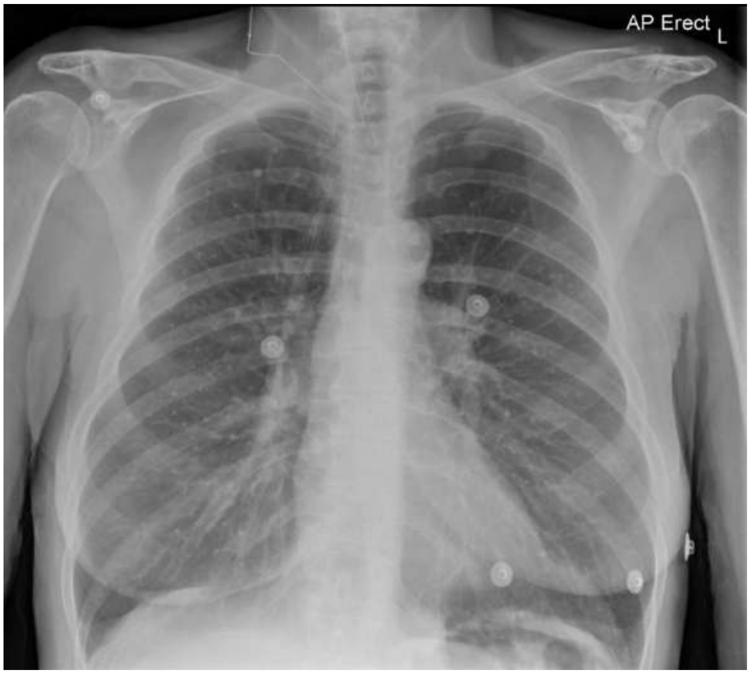
- keep cool, trim nails
- calamine lotion
- school exclusion: NICE Clinical Knowledge Summaries state the following: *Advise that the most infectious period is 1–2 days before the rash appears, but infectivity continues until all the lesions are dry and have crusted over (usually about 5 days after the onset of the rash).*
- immunocompromised patients and newborns with peripartum exposure should receive varicella zoster immunoglobulin (VZIG). If chickenpox develops then IV aciclovir should be considered

A common complication is secondary bacterial infection of the lesions

- NSAIDs may increase this risk
- whilst this commonly may manifest as a single infected lesion/small area of cellulitis, in a small number of patients invasive group A streptococcal soft tissue infections may occur resulting in necrotizing fasciitis

Rare complications include

- pneumonia
- encephalitis (cerebellar involvement may be seen)
- disseminated haemorrhagic chickenpox
- arthritis, nephritis and pancreatitis may very rarely be seen



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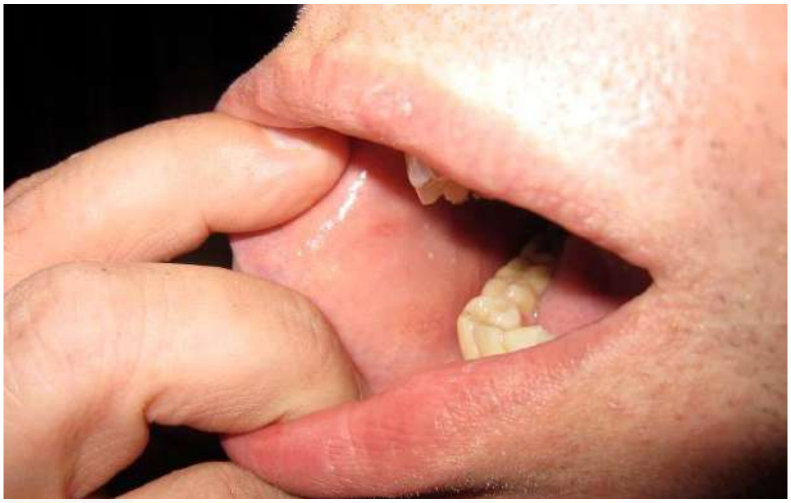
Chest x-ray showing miliary opacities secondary to healed varicella pneumonia. Multiple tiny calcific miliary opacities noted throughout both lungs. These are of uniform size and dense suggesting calcification. There is no focal lung parenchymal mass or cavitating lesion seen. The appearances are characteristic for healed varicella pneumonia.

# MEASLES

Measles is now rarely seen in the developed world following the adoption of immunisation programmes. Outbreaks are occasionally seen, particularly when vaccinations rates drop, for example after the MMR controversy of the early 2000s.

Overview
- RNA paramyxovirus
- spread by droplets
- infective from prodrome until 4 days after rash starts
- incubation period = 10-14 days

Features
- prodrome: irritable, conjunctivitis, fever
- Koplik spots (before rash): white spots ('grain of salt') on buccal mucosa
- rash: starts behind ears then to whole body, discrete maculopapular rash becoming blotchy & confluent



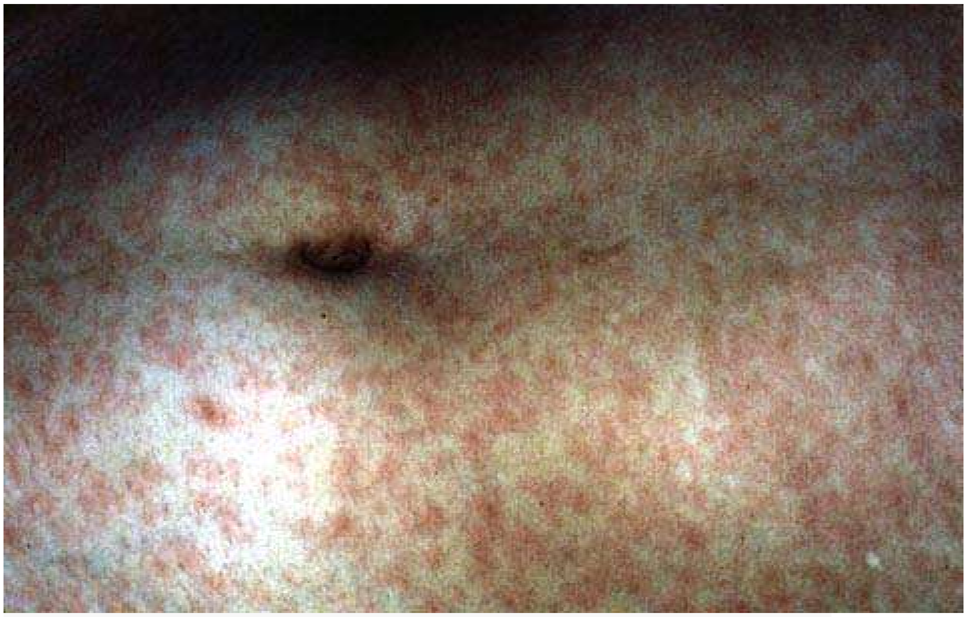
Koplik spots

Investigations
- IgM antibodies can be detected within a few days of rash onset

Management
- mainly supportive
- admission may be considered in immunosuppressed or pregnant patients
- notifiable disease → inform public health

Complications
- otitis media: the most common complication
- pneumonia: the most common cause of death
- encephalitis: typically occurs 1-2 weeks following the onset of the illness)
- subacute sclerosing panencephalitis: very rare, may present 5-10 years following the illness
- febrile convulsions

- keratoconjunctivitis, corneal ulceration
- diarrhoea
- increased incidence of appendicitis
- myocarditis



The rash typically starts behind the ears and then spreads to the whole body

Management of contacts

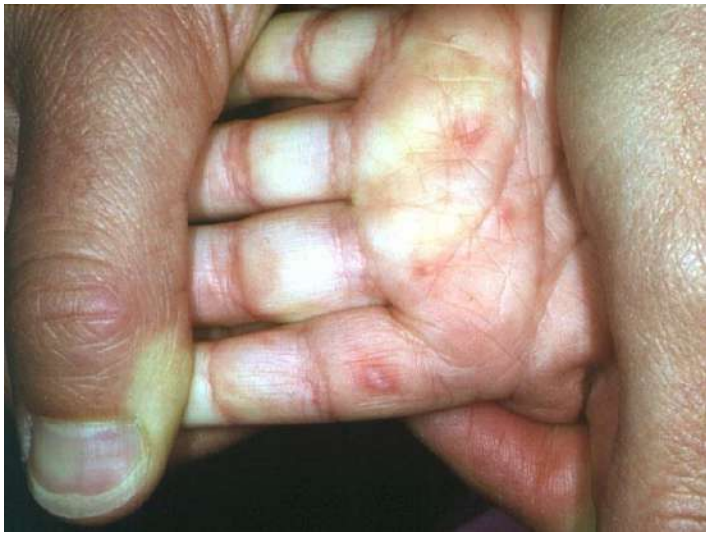
- if a child not immunized against measles comes into contact with measles then MMR should be offered (vaccine-induced measles antibody develops more rapidly than that following natural infection)
- this should be given within 72 hours

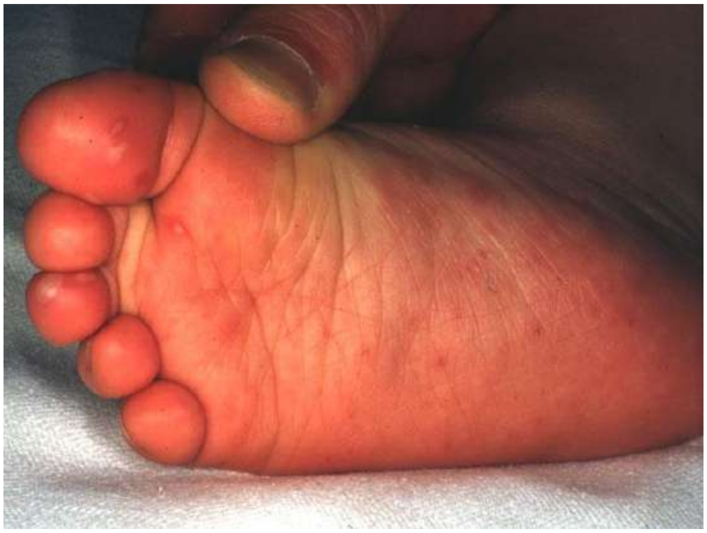
# HAND, FOOT AND MOUTH DISEASE

Hand, foot and mouth disease is a self-limiting condition affecting children. It is caused by the intestinal viruses of the Picornaviridae family (most commonly coxsackie A16 and enterovirus 71). It is very contagious and typically occurs in outbreaks at nursery

Clinical features

- mild systemic upset: sore throat, fever
- oral ulcers
- followed later by vesicles on the palms and soles of the feet





Management

- symptomatic treatment only: general advice about hydration and analgesia
- reassurance no link to disease in cattle
- children do not need to be excluded from school
    - the HPA recommends that children who are unwell should be kept off school until they feel better
    - they also advise that you contact them if you suspect that there may be a large outbreak.

# ENTEROVIRUSES

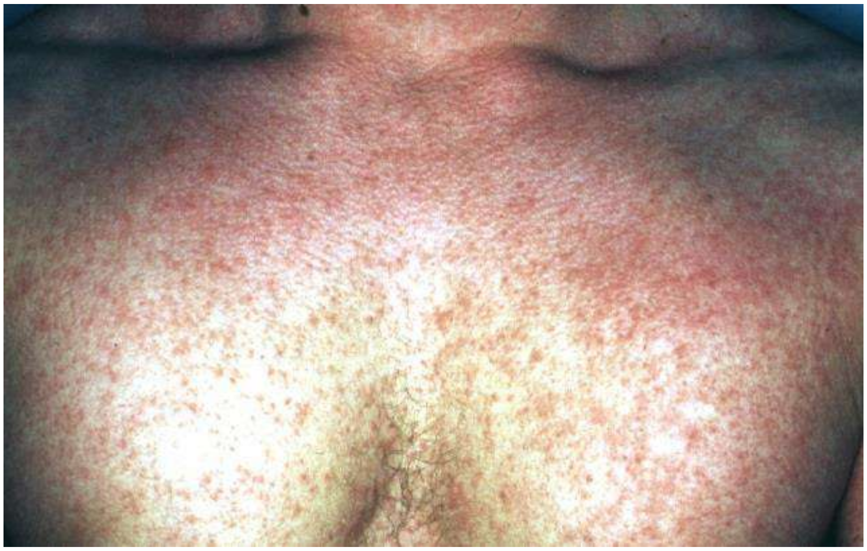
Enteroviruses are positive-sense single stranded RNA viruses. The family contains the Coxsackievirus, echovirus and rhinovirus as well as others. It is the most common cause of viral meningitis in the adult population but can cause a range of different diseases, in both adults and children. Although the range of diseases caused by these viruses is broad, notable disease entities include Hand, Foot and Mouth disease, herpangina and pericarditis.

# SCARLET FEVER

Scarlet fever is a reaction to erythrogenic toxins produced by Group A haemolytic streptococci (usually Streptococcus pyogenes). It is more common in children aged 2 - 6 years with the peak incidence being at 4 years.

Scarlet fever is spread via the respiratory route by inhaling or ingesting respiratory droplets or by direct contact with nose and throat discharges, (especially during sneezing and coughing).

Scarlet fever has an incubation period of 2-4 days and typically presents with:
- fever: typically lasts 24 to 48 hours
- malaise, headache, nausea/vomiting
- sore throat
- 'strawberry' tongue
- rash
    - fine punctate erythema ('pinhead') which generally appears first on the torso and spares the palms and soles
    - children often have a flushed appearance with circumoral pallor. The rash is often more obvious in the flexures
    - it is often described as having a rough 'sandpaper' texture
    - desquamination occurs later in the course of the illness, particularly around the fingers and toes



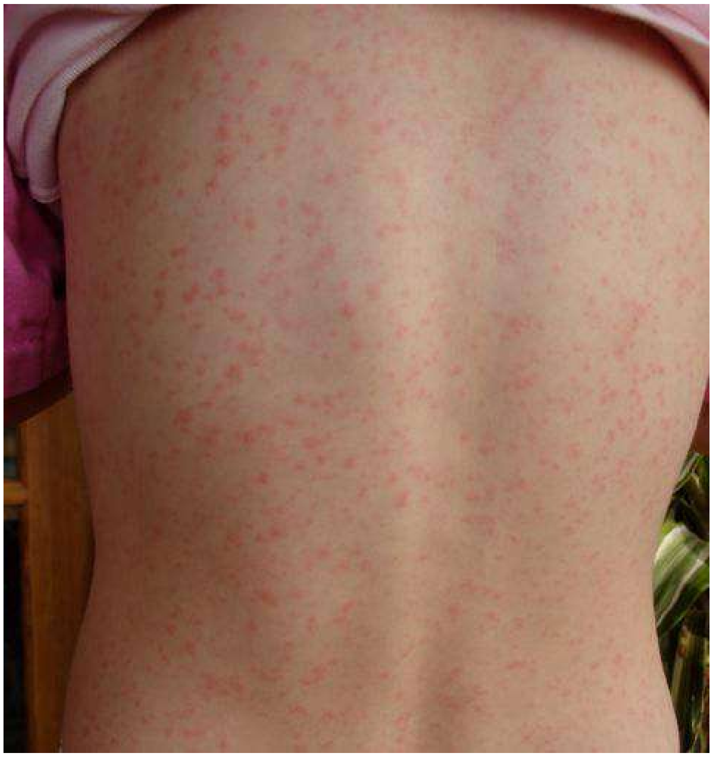
Diagnosis
- a throat swab is normally taken but antibiotic treatment should be commenced immediately, rather than waiting for the results

Management
- oral penicillin V for 10 days

- patients who have a penicillin allergy should be given azithromycin
- children can return to school 24 hours after commencing antibiotics
- scarlet fever is a notifiable disease

Scarlet fever is usually a mild illness but may be complicated by:

- otitis media: the most common complication
- rheumatic fever: typically occurs 20 days after infection
- acute glomerulonephritis: typically occurs 10 days after infection
- invasive complications (e.g. bacteraemia, meningitis, necrotizing fasciitis) are rare but may present acutely with life-threatening illness



# BRONCHIOLITIS

Bronchiolitis is a condition characterised by acute bronchiolar inflammation. Respiratory syncytial virus (RSV) is the pathogen in 75-80% of cases. NICE released guidelines on bronchiolitis in 2015. Please see the link for more details.

Epidemiology
- most common cause of a serious lower respiratory tract infection in < 1yr olds (90% are 1-9 months, with a peak incidence of 3-6 months). Maternal IgG provides protection to newborns against RSV
- higher incidence in winter

Basics
- respiratory syncytial virus (RSV) is the pathogen in 75-80% of cases
- other causes: mycoplasma, adenoviruses
- may be secondary bacterial infection
- more serious if bronchopulmonary dysplasia (e.g. Premature), congenital heart disease or cystic fibrosis

Features
- coryzal symptoms (including mild fever) precede:
- dry cough
- increasing breathlessness
- wheezing, fine inspiratory crackles (not always present)
- feeding difficulties associated with increasing dyspnoea are often the reason for hospital admission

NICE recommend immediate referral (usually by 999 ambulance) if they have any of the following:
- apnoea (observed or reported)
- child looks seriously unwell to a healthcare professional
- severe respiratory distress, for example grunting, marked chest recession, or a respiratory rate of over 70 breaths/minute
- central cyanosis
- persistent oxygen saturation of less than 92% when breathing air.

NICE recommend that clinicians 'consider' referring to hospital if any of the following apply:
- a respiratory rate of over 60 breaths/minute
- difficulty with breastfeeding or inadequate oral fluid intake (50-75% of usual volume 'taking account of risk factors and using clinical judgement')
- clinical dehydration.

Investigation
- immunofluorescence of nasopharyngeal secretions may show RSV

Management is largely supportive

- humidified oxygen is given via a head box and is typically recommended if the oxygen saturations are persistently < 92%
- nasogastric feeding may be needed if children cannot take enough fluid/feed by mouth
- suction is sometimes used for excessive upper airway secretions

# CROUP

Croup is a form of upper respiratory tract infection seen in infants and toddlers. It is characterised by stridor which is caused by a combination of laryngeal oedema and secretions. Parainfluenza viruses account for the majority of cases.

Epidemiology

- peak incidence at 6 months - 3 years
- more common in autumn

Features

- stridor
- barking cough (worse at night)
- fever
- coryzal symptoms

Clinical Knowledge Summaries (CKS) suggest using the following criteria to grade the severity*:

| Mild | Moderate | Severe |
|---|---|---|
| Occasional barking cough<br>No audible stridor at rest<br>No or mild suprasternal and/or intercostal recession<br>The child is happy and is prepared to eat, drink, and play | Frequent barking cough<br>Easily audible stridor at rest<br>Suprasternal and sternal wall retraction at rest<br>No or little distress or agitation<br>The child can be placated and is interested in its surroundings | Frequent barking cough<br>Prominent inspiratory (and occasionally, expiratory) stridor at rest<br>Marked sternal wall retractions<br>Significant distress and agitation, or lethargy or restlessness (a sign of hypoxaemia)<br>Tachycardia occurs with more severe obstructive symptoms and hypoxaemia |

CKS suggest admitting any child with moderate or severe croup. Other features which should prompt admission include:

- < 6 months of age
- known upper airway abnormalities (e.g. Laryngomalacia, Down's syndrome)
- uncertainty about diagnosis (important differentials include acute epiglottitis, bacterial tracheitis, peritonsillar abscess and foreign body inhalation)

Investigations

- the vast majority of children are diagnosed clinically
- however, if a chest x-ray is done:
    - a posterior-anterior view will show subglottic narrowing, commonly called the 'steeple sign'
    - in contrast, a lateral view in acute epiglottis will show swelling of the epiglottis - the 'thumb sign'

Management

- CKS recommend giving a single dose of oral dexamethasone (0.15mg/kg) to all children regardless of severity
- prednisolone is an alternative if dexamethasone is not available

Emergency treatment

- high-flow oxygen
- nebulised adrenaline

*these in turn are based partly on the Alberta Medical Association (2008) Guideline for the diagnosis and management of croup.

# HERPES SIMPLEX VIRUS

There are two strains of the herpes simplex virus (HSV) in humans: HSV-1 and HSV-2. Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap

Features

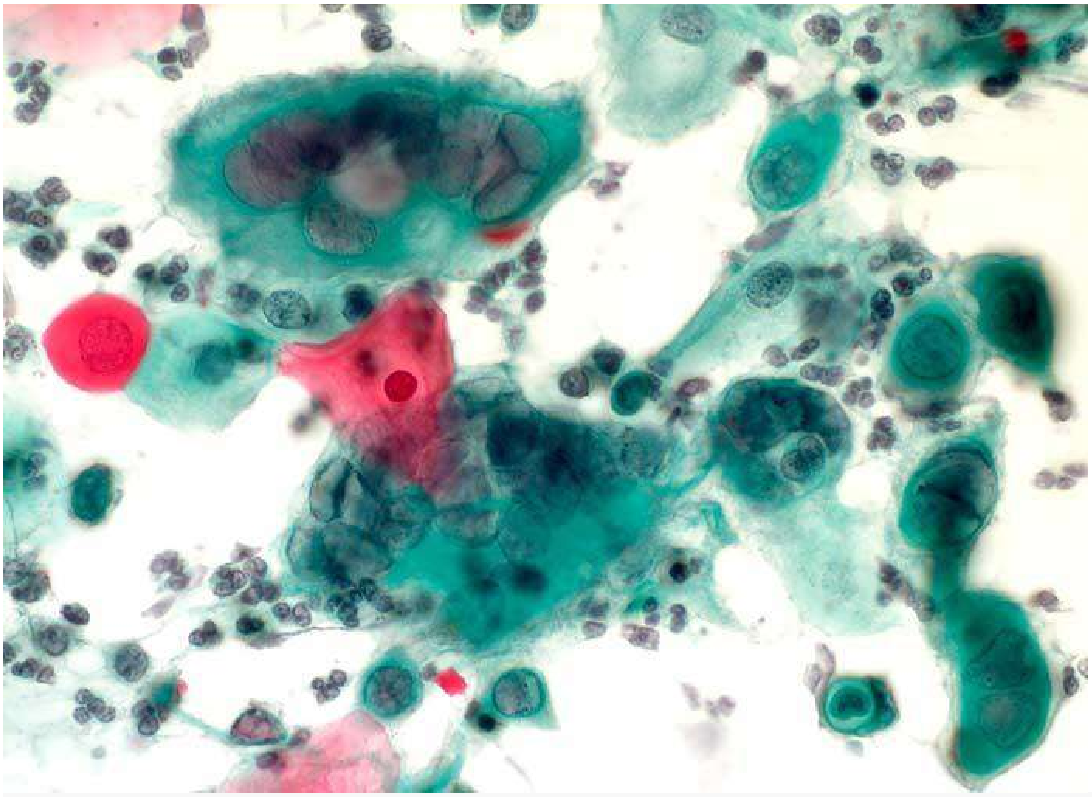
- primary infection: may present with a severe gingivostomatitis
- cold sores
- painful genital ulceration

Management

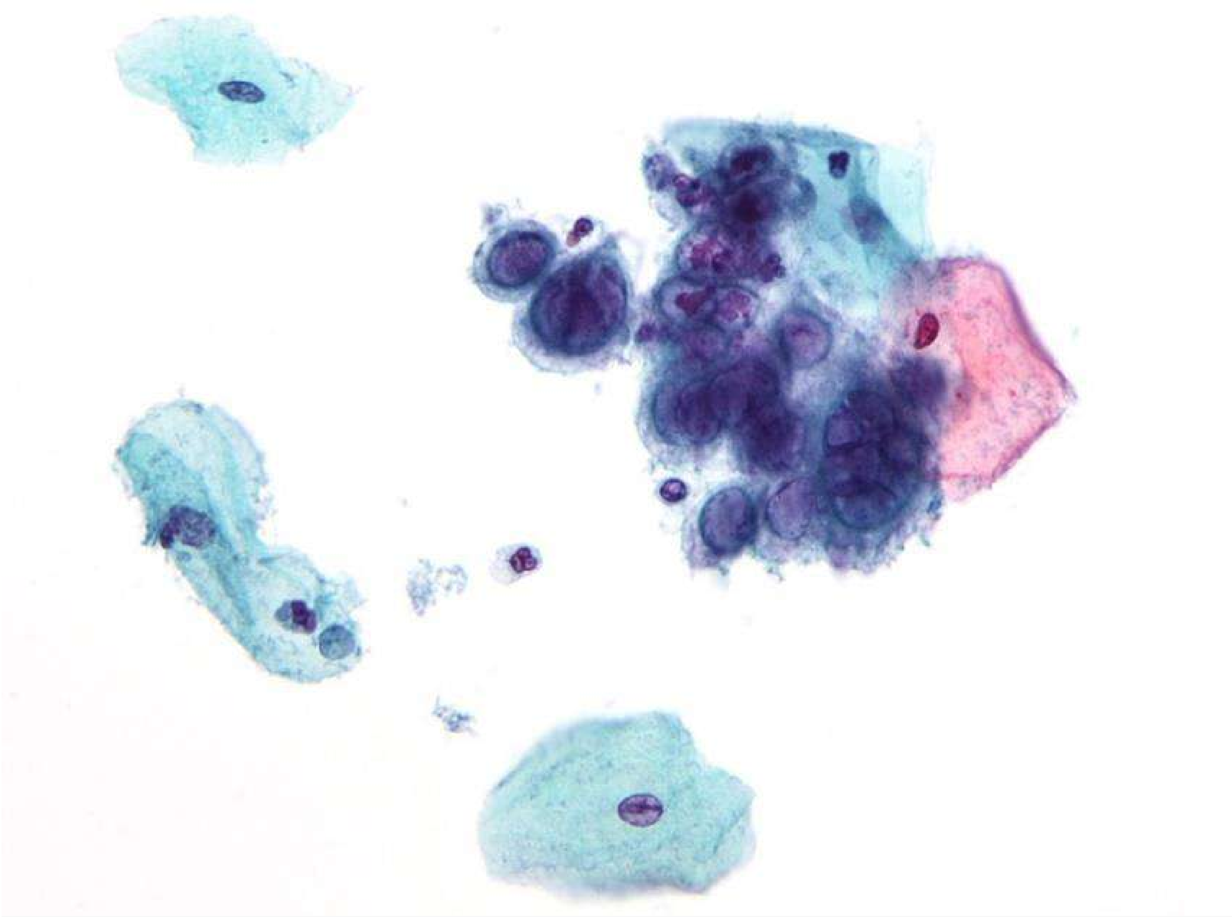
- gingivostomatitis: oral aciclovir, chlorhexidine mouthwash
- cold sores: topical aciclovir although the evidence base for this is modest
- genital herpes: oral aciclovir. Some patients with frequent exacerbations may benefit from longer term aciclovir

Pregnancy

- elective caesarean section at term is advised if a primary attack of herpes occurs during pregnancy at greater than 28 weeks gestation
- women with recurrent herpes who are pregnant should be treated with suppressive therapy and be advised that the risk of transmission to their baby is low



Pap smear. Multinucleated giant cells representing infection by the herpes simplex virus. Note the 3 M's; Multinucleation, Margination of the chromatin, Molding of the nuclei

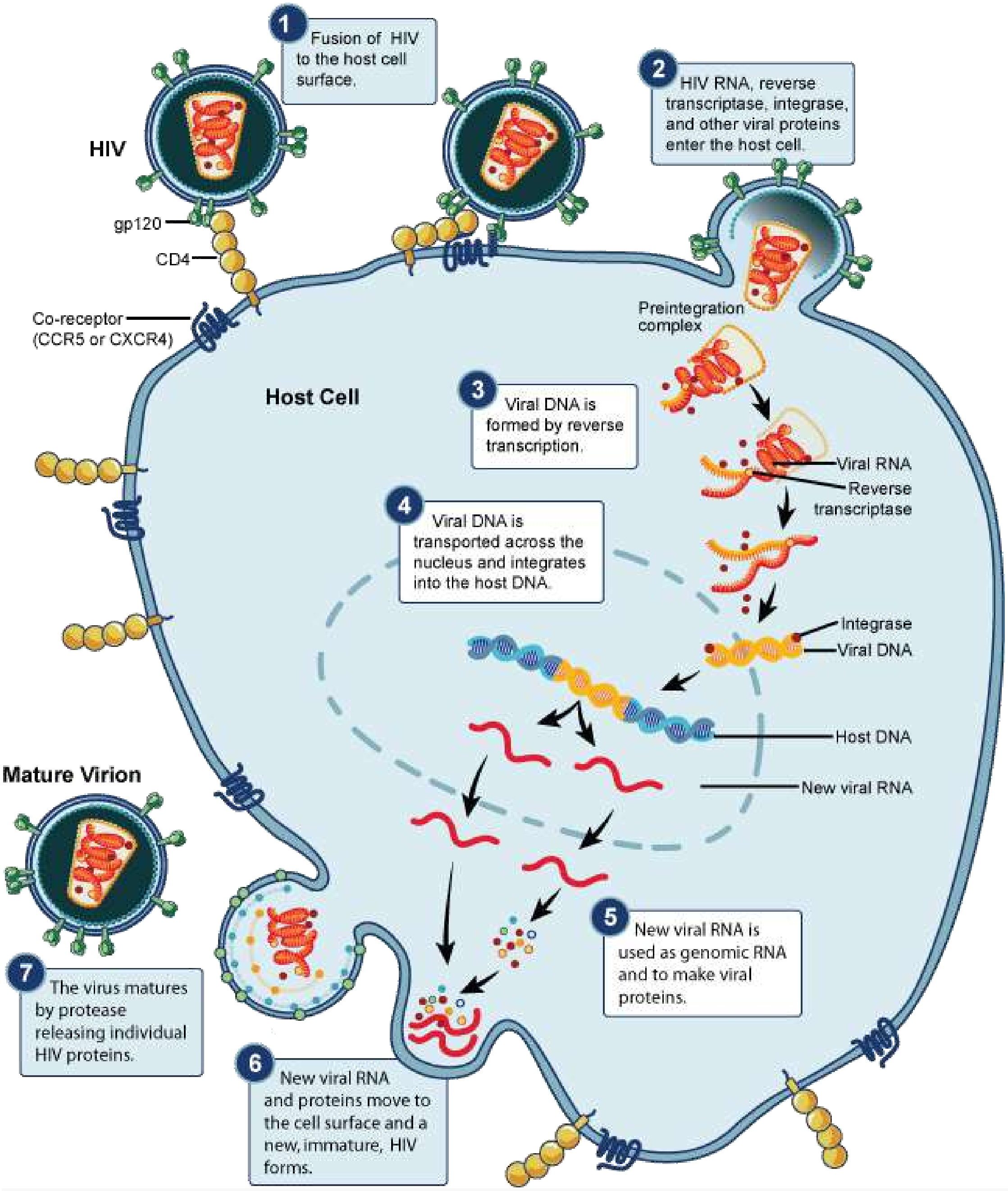


Further Pap smear showing the cytopathic effect of HSV (multi-nucleation, ground glass & marginated chromatin)

# HIV: IMMUNOLOGY

The following immunological changes are seen in progressive HIV:

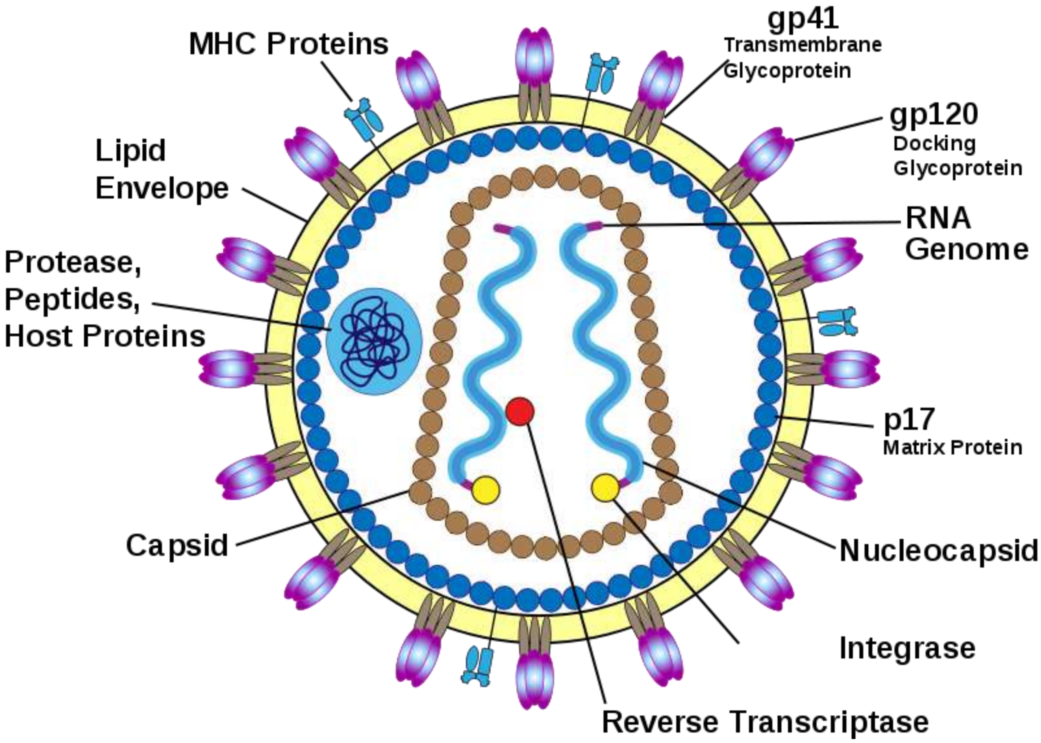
- reduction in CD4 count
- increase B2-microglobulin
- decreased IL-2 production
- polyclonal B-cell activation
- decrease NK cell function
- reduced delayed hypersensitivity responses


1
Fusion of HIV to the host cell surface.
HIV
gp120
CD4
Co-receptor (CCR5 or CXCR4)
2
HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell.
Preintegration complex
Host Cell
3
Viral DNA is formed by reverse transcription.
Viral RNA
Reverse transcriptase
4
Viral DNA is transported across the nucleus and integrates into the host DNA.
Integrase
Viral DNA
Host DNA
New viral RNA
Mature Virion
5
New viral RNA is used as genomic RNA and to make viral proteins.
7
The virus matures by protease releasing individual HIV proteins.
6
New viral RNA and proteins move to the cell surface and a new, immature, HIV forms.

An illustration model of the HIV Replication Cycle. Each step of the cycle is numbered and concisely described. Credit: NIAID

# HIV: THE VIRUS

Basics
- HIV is a RNA retrovirus of the lentivirus genus (lentiviruses are characterized by a long incubation period)
- two variants - HIV-1 and HIV-2
- HIV-2 is more common in west Africa, has a lower transmission rate and is thought to be less pathogenic with a slower progression to AIDS


MHC Proteins
gp41
Transmembrane Glycoprotein
gp120
Docking Glycoprotein
Lipid Envelope
RNA Genome
Protease, Peptides, Host Proteins
p17
Matrix Protein
Capsid
Nucleocapsid
Integrase
Reverse Transcriptase

Basics structure
- spherical in shape with two copies of single-stranded RNA enclosed by a capsid of the viral protein p24
- a matrix composed of viral protein p17 surrounds the capsid
- envelope proteins: gp120 and gp41
- pol gene encodes for viral enzymes reverse transcriptase, integrase and HIV protease

Cell entry
- HIV can infect CD4 T cells, macrophages and dendritic cells
- gp120 binds to CD4 and CXCR4 on T cells and CD4 and CCR5 on macrophages
- mutations in CCR5 can give immunity to HIV

Replication
- after entering a cell the enzyme reverse transcriptase creates dsDNA from the RNA for integration into the host cell's genome

# ACUTE EPIGLOTTITIS

Acute epiglottitis is rare but serious infection caused by Haemophilus influenzae type B. Prompt recognition and treatment is essential as airway obstruction may develop. Epiglottitis was generally considered a disease of childhood but in the UK it is now more common in adults due to the immunisation programme. The incidence of epiglottitis has decreased since the introduction of the Hib vaccine.

Features

- rapid onset
- high temperature, generally unwell
- stridor
- drooling of saliva

Investigations

- chest x-ray
- a lateral view in acute epiglottis will show swelling of the epiglottis - the 'thumb sign'
- in contrast, a posterior-anterior view in croup will show subglottic narrowing, commonly called the 'steeple sign'

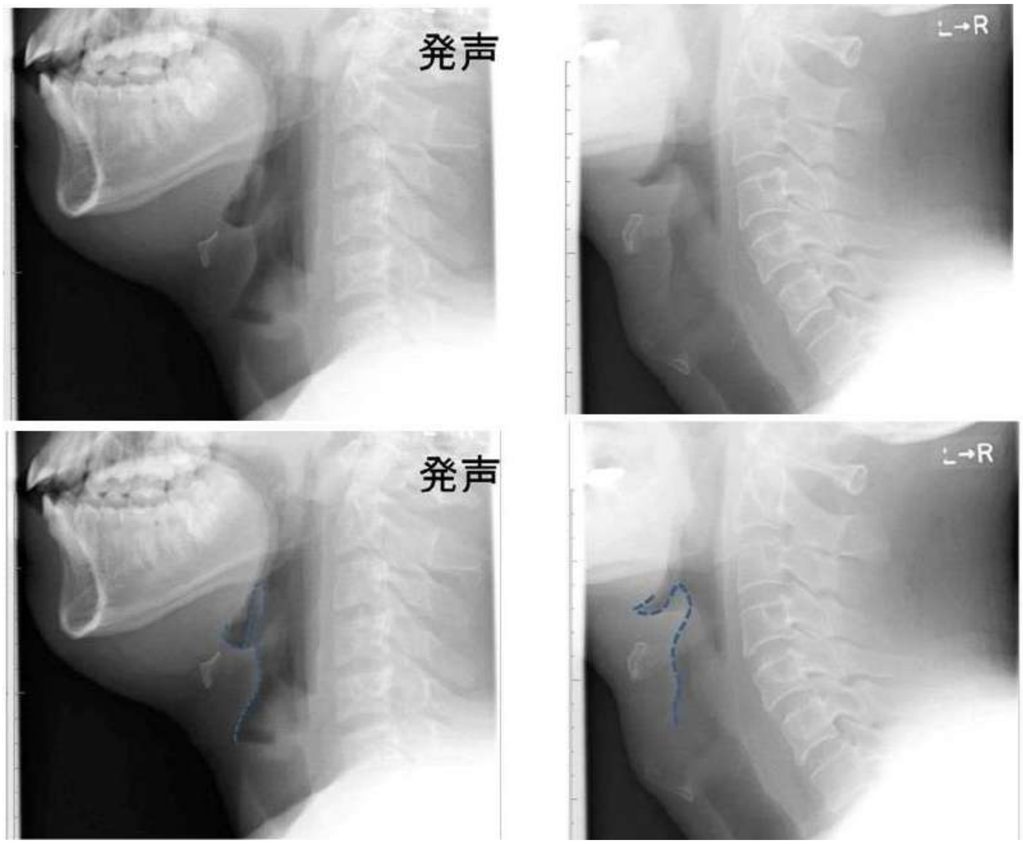


Image showing a normal epiglottis on the left and an inflamed one on the right.  Annotated in blue in the bottom two images

# CHOLANGITIS

- Combination of bacterial infection and biliary obstruction
- Most common organisms are: (most frequent at top of list)
  Escherichia coli
  Klebsiella species
  Enterococcus species
  Streptococcus species

**Clinical features**
*Charcot's triad:*
Fever (90% cases)
Right upper quadrant pain
Jaundice

Reynolds pentad: Above plus confusion and hypotension

**Investigations**
- USS 1st line
- CT scan
- ERCP: may be 1st line if high clinical suspicion and suitable for treatment

**Treatment**
- ERCP -usually after 72 hours of antibiotics
- Percutaneous transhepatic cholangiogram and biliary drain

# POST-SPLENECTOMY SEPSIS

Hyposplenism may complicate certain medical conditions where splenic atrophy occurs or may be the result of medical intervention such as splenic artery embolization and splenectomy for trauma. Diagnosis of hyposplenism is difficult and whilst there may be peripheral markers of the splenectomised state (e.g. Howell-Jolly bodies) these are neither 100% sensitive or specific. The most sensitive test is a radionucleotide labelled red cell scan.

Hyposplenism, by whatever mechanism it occurs dramatically increases the risk of post-splenectomy sepsis, particularly with encapsulated organisms. Since these organisms may be opsonised, but this then goes undetected at an immunological level due to loss of the spleen. For this reason, individuals are recommended to be vaccinated and have antibiotic prophylaxis.

Key recommendations
- All those with hyposplenism or may become so (such as prior to an elective splenectomy) should receive pneumococcal, Haemophilus type b and meningococcal type C vaccines. These should be

administered 2 weeks prior to splenectomy or two weeks following splenectomy. The vaccine schedule for meningococcal disease essentially consists of a dose of Men C and Hib at 2 weeks and then a dose of the MenACWY vaccine one month later. Those aged under 2 may require a booster at 2 years. A dose of pneumococcal polyvalent polysaccharide vaccine (PPV) is given at two weeks. A conjugated vaccine (PCV) is offered to young children. The PCV is more immunogenic but covers fewer serotypes. Boosting PPV is either guided by serological measurements (where available) or by routine boosting doses at 5 yearly intervals.
- Annual influenza vaccination is recommended in all cases
- Antibiotic prophylaxis is offered to all. The risk of post-splenectomy sepsis is greatest immediately following splenectomy and in those aged less than 16 years or greater than 50 years. Individuals with a poor response to pneumococcal vaccination are another high-risk group. High-risk individuals should be counselled to take penicillin or macrolide prophylaxis. Those at low risk may choose to discontinue therapy. All patients should be advised about taking antibiotics early in the case of intercurrent infections.
- Asplenic individuals travelling to malaria endemic areas are at high risk and should have both pharmacological and mechanical protection.

**Dosing**
Penicillin V 500mg BD or amoxicillin 250mg BD

**References**

Davies J et al. Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen: Prepared on behalf of the British Committee for Standards in Haematology by a Working Party of the Haemato-Oncology Task Force. British Journal of Haematology 2011 (155): 308317.

# MECKEL'S DIVERTICULUM

Meckel's diverticulum is a congenital diverticulum of the small intestine. It is a remnant of the omphalomesenteric duct (also called the vitellointestinal duct) and contains ectopic ileal, gastric or pancreatic mucosa

Rule of 2s
- occurs in 2% of the population
- is 2 feet from the ileocaecal valve
- is 2 inches long

Presentation (usually asymptomatic)
- abdominal pain mimicking appendicitis
- rectal bleeding
- Meckel's diverticulum is the most common cause of painless massive GI bleeding requiring a transfusion in children between the ages of 1 and 2 years

- intestinal obstruction
- secondary to an omphalomesenteric band (most commonly), volvulus and intussusception

Management
- removal if narrow neck or symptomatic. Options are between wedge excision or formal small bowel resection and anastomosis.

Pathophysiology
- normally, in the foetus, there is an attachment between the vitellointestinal duct and the yolk sac. This disappears at 6 weeks gestation
- the tip is free in the majority of cases
- associated with enterocystomas, umbilical sinuses, and omphaloileal fistulas.
- arterial supply: omphalomesenteric artery.
- typically lined by ileal mucosa but ectopic gastric mucosa can occur, with the risk of peptic ulceration. Pancreatic and jejunal mucosa can also occur.

# APPENDICITIS IN CHILDREN

Appendicitis is one of the most common acute surgical problems facing children. Diagnosis is often made difficult by a presentation which is far from the classically history of:
- central abdominal pain which later radiates to the right iliac fossa
- low-grade pyrexia
- minimal vomiting

Children who are younger or have a retrocaecal/pelvic appendix are more likely to present in an atypical way

Appendicitis is uncommon in children under 4 years old but in this group often presents with perforation

# PYLORIC STENOSIS

Pyloric stenosis typically presents in the second to fourth weeks of life with vomiting, although rarely may present later at up to four months. It is caused by hypertrophy of the circular muscles of the pylorus.

Epidemiology
- incidence of 4 per 1,000 live births
- 4 times more common in males
- 10-15% of infants have a positive family history

- first-borns are more commonly affected

Features
- 'projectile' vomiting, typically 30 minutes after a feed
- constipation and dehydration may also be present
- a palpable mass may be present in the upper abdomen
- hypochloraemic, hypokalaemic alkalosis due to persistent vomiting

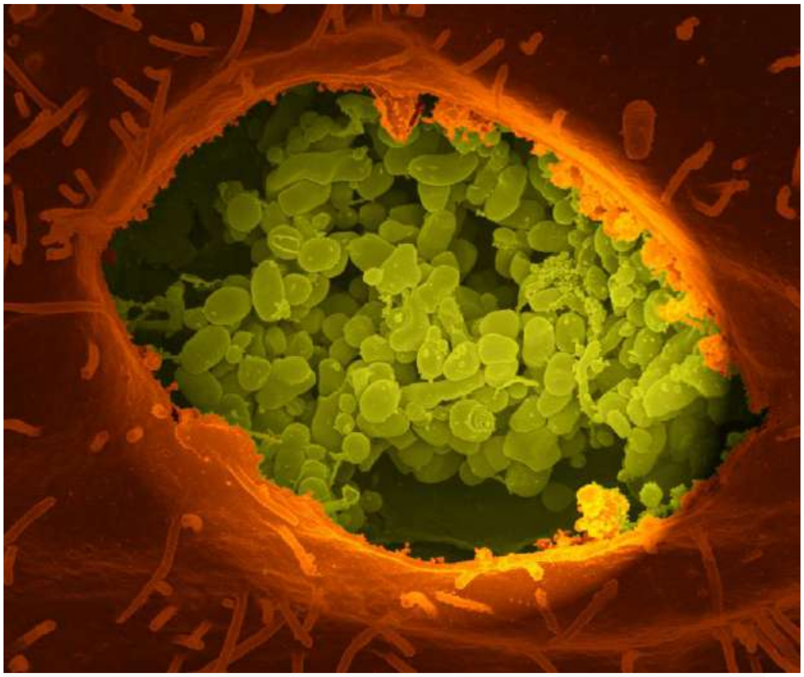
Diagnosis is most commonly made by ultrasound.

Management is with Ramstedt pyloromyotomy.

# RICKETTSIAE

Rickettsiae are Gram-negative obligate intracellular parasites. Types of rickettsiae cause a variety of diseases that are typically characterised by fever, headache and rash. A notable exception is Q fever (cause by Coxiella burnetti which causes pneumonia but no rash. The Weil-Felix reaction is positive except in Q fever. Rickettsial diseases are all treated with tetracyclines.

| Disease | Cause | Vector | Notes |
|---|---|---|---|
| Rocky Mountain spotted fever | Rickettsia ricketsii | Tick | Headache and fever are common<br>Rash starts on the peripheries (wrist, ankles) before spreading centrally. It is initially maculopapular before becoming vasculitic<br>Endemic to east coast of US |
| Q fever | Coxiella burnetti | No vector | No rash but causes pneumonia |
| Endemic typhus | Rickettsia typhi | Flea | Rash starts centrally then spreads to the peripheries |
| Epidemic typhus | Rickettsia prowazekii | Human body louse | |
| Ehrlichliosis | Ehrlichia | Tick | |



A dry fracture of a Vero cell exposing the contents of a vacuole where *Coxiella burnetti* are busy growing. Note the intracellular nature of the organism. Credit: NIAID

# HELMINTHS

## Nematodes (roundworms)

| Worm | Notes | Treatment |
|---|---|---|
| *Strongyloides stercoralis* | Larvae are present in soil and gain access to the body by penetrating the skin<br>Features include diarrhoea, abdominal pain, papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks, larva currens: pruritic, linear, urticarial rash, if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered | Ivermectin and -bendazoles are used |
| *Enterobius vermicularis* (pinworm) | Threadworm infestation is asymptomatic in around 90% of cases, possible features include perianal itching, particularly at night; girls may have vulval symptoms<br>Diagnosis may be made by the applying sticky plastic tape to the perianal area and sending it to the laboratory for microscopy to see the eggs | -bendazoles |
| *Ancylostoma duodenale*, *Necator americanus* (hookworms) | Larvae penetrate skin of feet; gastrointestinal infection → anaemia<br>Thin-shelled ova | -bendazoles |

| Worm | Notes | Treatment |
|---|---|---|
| *Loa loa* | Transmission by deer fly and mango fly<br><br>Causes red itchy swellings below the skin called 'Calabar swellings', may be observed when crossing conjunctivae | Diethylcarbamazine |
| *Trichinella spiralis* | Typically develops after eating raw pork<br><br>Features include fever, periorbital oedema and myositis (larvae encyst in muscle) | -bendazoles |
| *Onchocerca volvulus* | Causes 'river blindness'. Spread by female blackflies<br><br>Features include blindness, hyperpigmented skin and possible allergic reaction to microfilaria | Ivermectin<br>r**IVER**blindness = **IVER**mectin |
| *Wuchereria bancrofti* | Transmission by female mosquito<br><br>Causes blockage of lymphatics → elephantiasis | Diethylcarbamazine |
| *Toxocara canis* (dog roundworm) | Transmitted through ingestion of infective eggs.<br><br>Features include visceral larva migrans and retinal granulomas<br>VISCious dogs → blindness | Diethylcarbamazine |
| *Ascaris lumbricoides* (giant roundworm) | Eggs are visible in faeces<br><br>May cause intestinal obstruction and occasional migrate to lung (Loffler's syndrome) | -bendazoles |

### Cestodes (tapeworms)

| Worm | Notes | Treatment |
|---|---|---|
| *Echinococcus granulosus* | Transmission through ingestion of eggs in dog faeces. Definite host is dog, which ingests hydatid cysts from sheep, who act as an intermediate host. Often seen in farmers.<br><br>Features include liver cysts and anaphylaxis if cyst ruptures (e.g. during surgical removal) | -bendazoles |
| *Taenia solium* | Often transmitted after eating undercooked pork. Causes cysticercosis and neurocysticercosis, mass lesions in the brain 'swiss cheese appearance' | -bendazoles |

### Trematodes (flukes)

| Worm | Notes | Treatment |
|---|---|---|
| *Schistosoma haematobium* | Hosted by snails, which release cercariae that penetrate skin. Causes 'swimmer's itch' - frequency, haematuria. Risk factor for squamous cell bladder cancer | Praziquantel |

| Worm | Notes | Treatment |
|---|---|---|
| *Paragonimus westermani* | Caused by undercooked crabmeat, results in secondary bacterial infection of lungs | Praziquantel |
| *Clonorchis sinensis* | Caused by undercooked fish<br>Features include biliary tract inflammation. Known risk factor for cholangiocarcinoma | Praziquantel |
| *Fasciola hepatica* (the liver fluke) | May cause biliary obstruction | Triclabendazole |

# WUCHERERIA BANCROFTI

- Parasitic filarial nematode
- Accounts for 90% of cases of filariasis
- Usually diagnosed by blood smears
- Usually transmitted by mosquitos
- Treatment is with diethylcarbamazine

# THREADWORMS

Infestation with threadworms (Enterobius vermicularis, sometimes called pinworms) is extremely common amongst children in the UK. Infestation occurs after swallowing eggs that are present in the environment.

Threadworm infestation is asymptomatic in around 90% of cases, possible features include:
- perianal itching, particularly at night
- girls may have vulval symptoms

Diagnosis may be made by the applying Sellotape to the perianal area and sending it to the laboratory for microscopy to see the eggs. However, most patients are treated empirically and this approach is supported in the CKS guidelines.

Management
- CKS recommend a combination of anthelmintic with hygiene measures for all members of the household
- mebendazole is used first-line for children > 6 months old. A single dose is given unless infestation persists

# CUTANEOUS LARVA MIGRANS

Cutaneous Larva Migrans is caused by the infection of the dog hook worm *Ancyclostoma Braziliense*.

Man is an accidental dead end host and so the larva is unable to migrate to the lungs and intestine. The intensely itchy trial is a result of the subcutaneous migration of the frustrated larva.

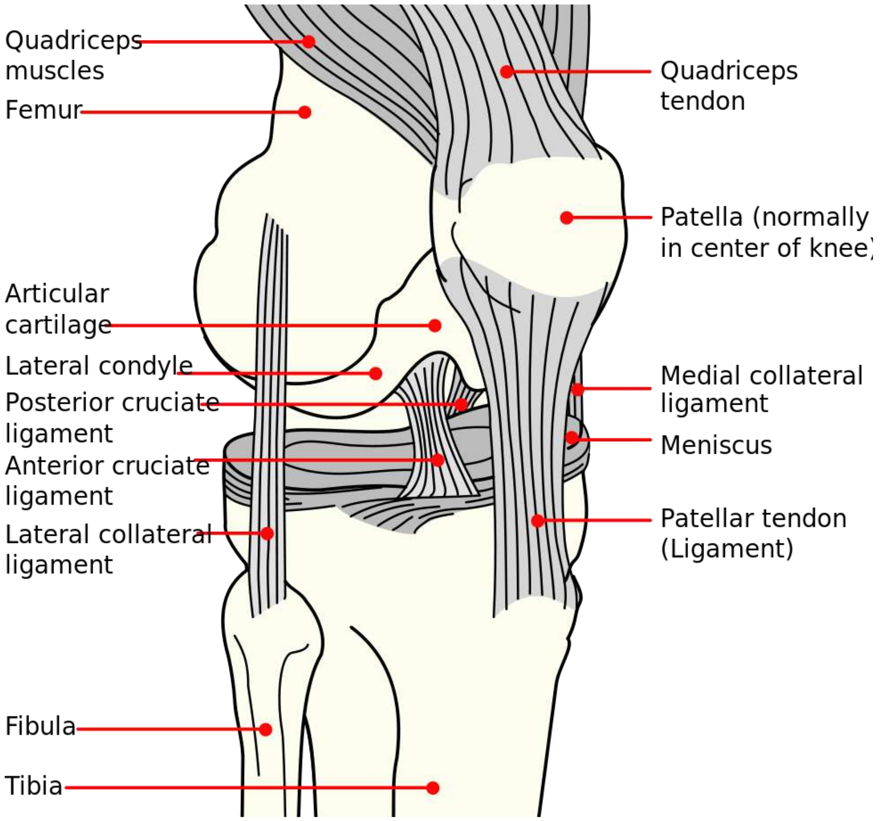
Management is with Albendazole or Ivermectin.

# KNEE PROBLEMS: CHILDREN AND YOUNG ADULTS

The table below summarises the key features of common knee problems:

| Condition | Key features |
|---|---|
| **Chondromalacia patellae** | Softening of the cartilage of the patella<br>Common in teenage girls<br>Characteristically anterior knee pain on walking up and down stairs and rising from prolonged sitting<br>Usually responds to physiotherapy |
| **Osgood-Schlatter disease (tibial apophysitis)** | Seen in sporty teenagers<br>Pain, tenderness and swelling over the tibial tubercle |
| **Osteochondritis dissecans** | Pain after exercise<br>Intermittent swelling and locking |
| **Patellar subluxation** | Medial knee pain due to lateral subluxation of the patella<br>Knee may give way |
| **Patellar tendonitis** | More common in athletic teenage boys<br>Chronic anterior knee pain that worsens after running<br>Tender below the patella on examination |

Referred pain may come from hip problems such as slipped upper femoral epiphysis


Quadriceps muscles
Femur
Quadriceps tendon
Patella (normally in center of knee)
Articular cartilage
Lateral condyle
Posterior cruciate ligament
Anterior cruciate ligament
Lateral collateral ligament
Medial collateral ligament
Meniscus
Patellar tendon (Ligament)
Fibula
Tibia

# KAWASAKI DISEASE

Kawasaki disease is a type of vasculitis which is predominately seen in children. Whilst Kawasaki disease is uncommon it is important to recognise as it may cause potentially serious complications, including coronary artery aneurysms.

Features
- high-grade fever which lasts for > 5 days. Fever is characteristically resistant to antipyretics
- conjunctival injection
- bright red, cracked lips
- strawberry tongue
- cervical lymphadenopathy
- red palms of the hands and the soles of the feet which later peel

Kawasaki disease is a clinical diagnosis as there is no specific diagnostic test.

Management
- high-dose aspirin
- Kawasaki disease is one of the few indications for the use of aspirin in children. Due to the risk of Reye's syndrome aspirin is normally contraindicated in children
- intravenous immunoglobulin
- echocardiogram (rather than angiography) is used as the initial screening test for coronary artery aneurysms

Complications
- coronary artery aneurysm

# ONCOGENES

Oncogenes are cancer promoting genes that are derived from normal genes (proto-oncogenes). Proto-oncogenes play an important physiological role in cellular growth and differentiation. A 'gain of function' results in an increased risk of cancer. Only one mutated copy of the gene is needed for cancer to occur - a dominant effect. They are implicated in the development of up to 20% of human cancers.

Proto-oncogenes may become oncogenes via the following processes:
- Mutation (point mutation)
- Chromosomal translocation
- Increased protein expression

**Examples**

| Gene | Category | Associated cancers |
|---|---|---|
| ABL | Cytoplasmic tyrosine kinase | Chronic myeloid leukaemia |
| c-MYC | Transcription factor | Burkitt's lymphoma |
| n-MYC | Transcription factor | Neuroblastoma |
| BCL-2 | Apoptosis regulator protein | Follicular lymphoma |
| RET | Tyrosine kinase receptor | Multiple endocrine neoplasia (types II and III) |
| RAS | G-protein | Many cancers especially pancreatic |
| erb-B2 (HER2/neu) | Tyrosine kinase receptor | Breast and ovarian cancer |

**How are they different from tumour supressory genes?**

Tumour suppressor genes restrict or repress cellular proliferation in normal cells. Their inactivation through mutation or germ line incorporation is implicated in renal, colonic, breast, bladder and many other cancers. One of the best known tumour suppressor genes is p53. p53 gene offers protection by causing apoptosis of damaged cells. Other well known genes include BRCA 1 and 2.

Tumor suppressor genes - loss of function results in an increased risk of cancer

Oncogenes - gain of function results in an increased risk of cancer

# TUMOUR SUPPRESSOR GENES

Basics
- genes which normally control the cell cycle
- loss of function results in an increased risk of cancer
- both alleles must be mutated before cancer occurs

**Examples**

| Gene | Associated cancers |
|---|---|
| p53 | Common to many cancers, Li-Fraumeni syndrome |
| APC | Colorectal cancer |
| BRCA1 | Breast and ovarian cancer |
| BRCA2 | Breast and ovarian cancer |
| NF1 | Neurofibromatosis |
| Rb | Retinoblastoma |
| WT1 | Wilm's tumour |
| Multiple tumor suppressor 1 (MTS-1, p16) | Melanoma |

Tumour suppressor genes - loss of function results in an increased risk of cancer

Oncogenes - gain of function results in an increased risk of cancer

# p53

p53 is a tumour suppressor gene located on chromosome 17p. It is the most commonly mutated gene in breast, colon and lung cancer

p53 is thought to play a crucial role in the cell cycle, preventing entry into the S phase until DNA has been checked and repaired. It may also be a key regulator of apoptosis

**Li-Fraumeni syndrome** is a rare autosomal dominant disorder characterised by the early onset of a variety of cancers such as sarcomas and breast cancer. It is caused by mutation in the p53 gene

# WILMS' TUMOUR

Wilms' nephroblastoma is one of the most common childhood malignancies. It typically presents in children under 5 years of age, with a median age of 3 years old.

Associations
- Beckwith-Wiedemann syndrome
- as part of WAGR syndrome with Aniridia, Genitourinary malformations, mental Retardation
- hemihypertrophy
- around one-third of cases are associated with a loss-of-function mutation in the WT1 gene on chromosome 11

Features

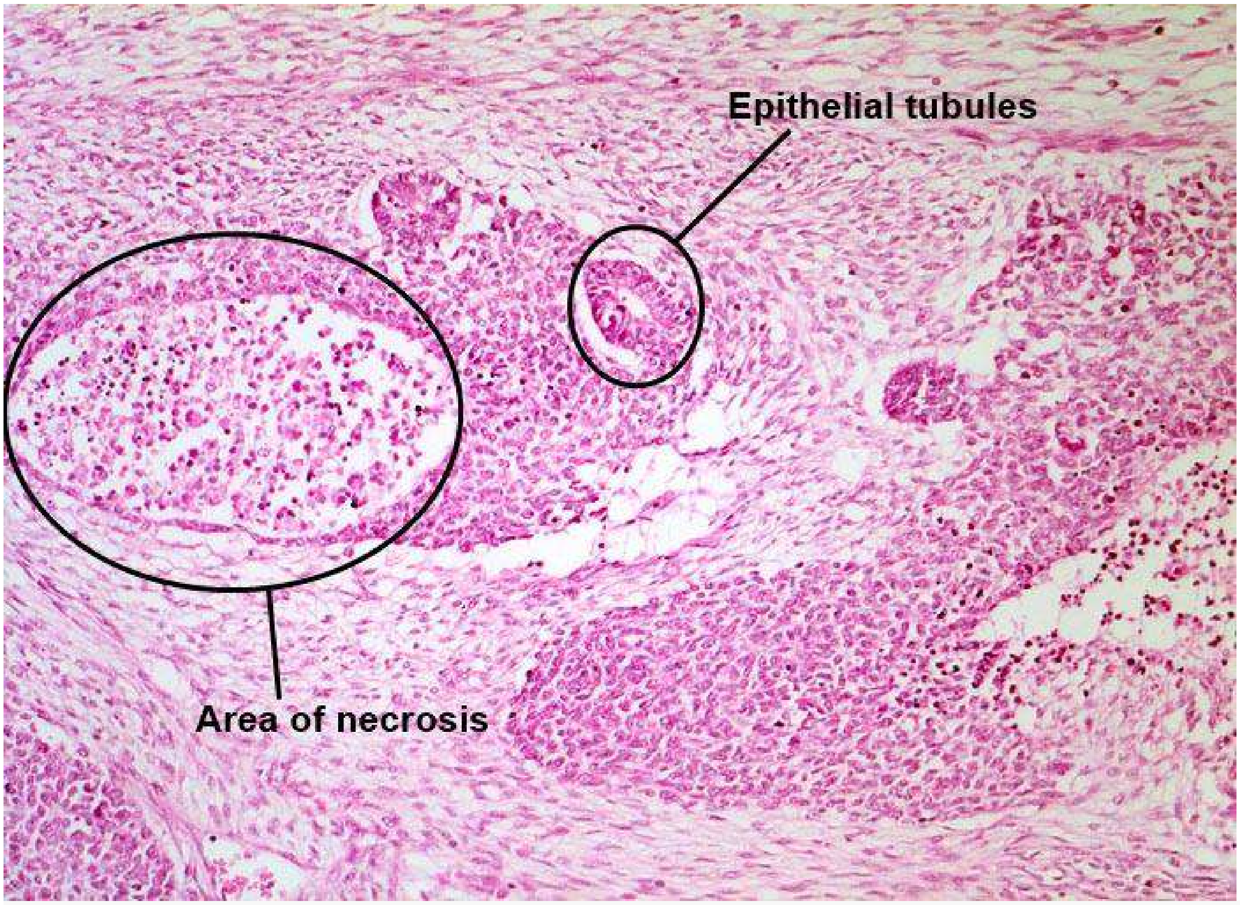
- abdominal mass (most common presenting feature)
- painless haematuria
- flank pain
- other features: anorexia, fever
- unilateral in 95% of cases
- metastases are found in 20% of patients (most commonly lung)

Referral

- children with an unexplained enlarged abdominal mass in children - possible Wilm's tumour - arrange paediatric review with 48 hours

Management

- nephrectomy
- chemotherapy
- radiotherapy if advanced disease
- prognosis: good, 80% cure rate



Histological features include epithelial tubules, areas of necrosis, immature glomerular structures, stroma with spindle cells and small cell blastomatous tissues resembling the metanephric blastema

# CNS TUMOURS

- 60% = Glioma and metastatic disease
- 20% = Meningioma
- 10% = Pituitary lesions

In paediatric practice medulloblastomas (neuroectodermal tumours) were the commonest lesions, astrocytomas now account for the majority.

Tumours arising in right temporal and frontal lobe may reach considerable size before becoming symptomatic. Whereas tumours in the speech and visual areas will typically produce early symptoms.

**Diagnosis**

MRI Scanning provides the best resolution.

**Treatment**

- Usually surgery, even if tumour cannot be completely resected conditions such as rising ICP can be addressed with tumour debulking and survival and quality of life prolonged.
- Curative surgery can usually be undertaken with lesions such as meningiomas. Gliomas have a marked propensity to invade normal brain and resection of these lesions is nearly always incomplete.

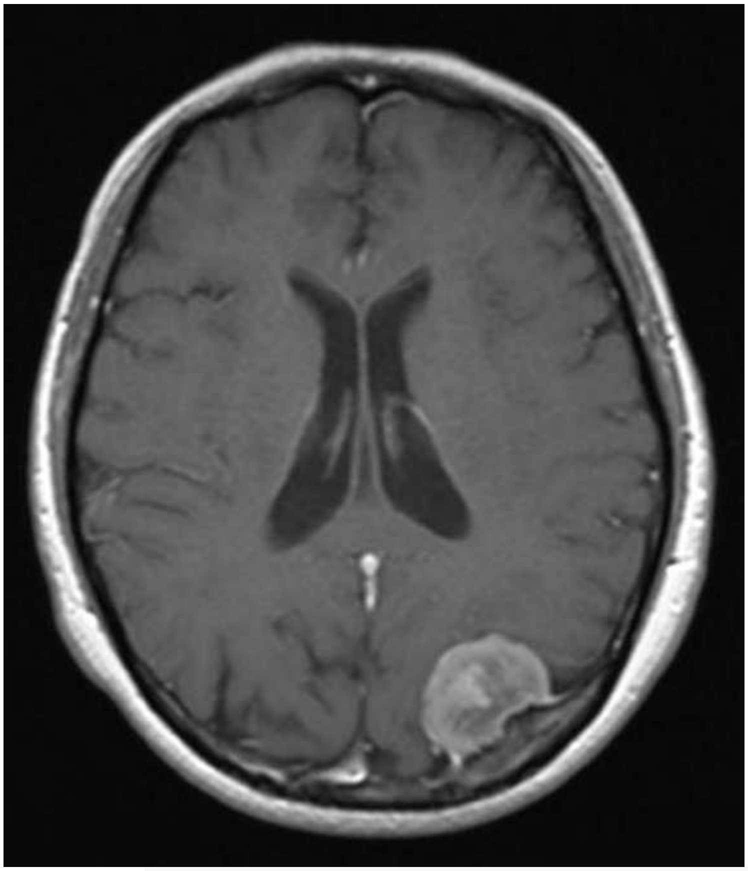
# BRAIN TUMOURS

The majority of adult tumours are supratentorial, where as the majority of childhood tumours are infratentorial.

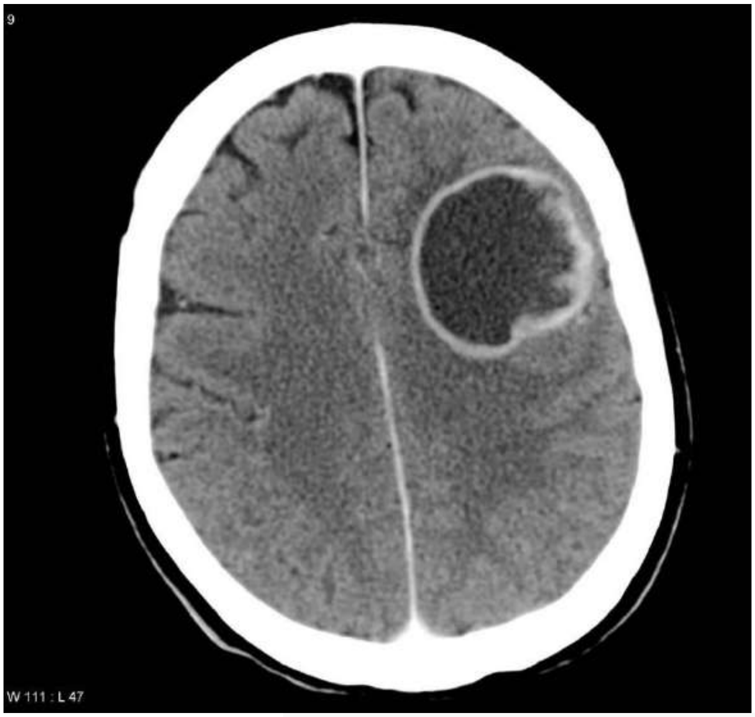
| Type of tumour | Features |
|---|---|
| Metastases | Metastatic brain cancer is the most common form of brain tumours. They are often multiple and not treatable with surgical intervention.<br>Tumours that most commonly spread to the brain include:<br>• lung (most common)<br>• breast<br>• bowel<br>• skin (namely melanoma)<br>• kidney |
| Gliolastoma multiforme | • Glioblastoma is the most common primary tumour in adults and is associated with a poor prognosis (~ 1yr).<br>• On imaging they are solid tumours with central necrosis and a rim that enhances |

| Type of tumour | Features |
|---|---|
| | with contrast. Disruption of the blood-brain barrier and therefore are associated with vasogenic oedema.<br>• Histology: Pleomorphic tumour cells border necrotic areas<br>• Treatment is surgical with postoperative chemotherapy and/or radiotherapy. Dexamethasone is used to treat the oedema. |
| Meningioma | • The second most common primary brain tumour in adults<br>• Meningiomas are typically benign, extrinsic tumours of the central nervous system. They arise from the dura mater of the meninges and cause symptoms by compression rather than invasion.<br>• They typically are located at the falx cerebri, superior sagittal sinus, convexity or skull base.<br>• Histology: Spindle cells in concentric whorls and calcified psammoma bodies<br>• Investigation is with CT (will show contrast enhancement) and MRI, and treatment will involve either observation, radiotherapy or surgical resection. |
| Vestibular schwannoma | • A vestibular schwannoma (previously termed acoustic neuroma) is a benign tumour arising from the eighth cranial nerve (vestibulocochlear nerve). Often seen in the cerebellopontine angle. It presents with hearing loss, facial nerve palsy (due to compression of the nearby facial nerve) and tinnitus.<br>• Neurofibromatosis type 2 is associated with bilateral vestibular schwannomas.<br>• Histology: Antoni A or B patterns are seen. Verocay bodies (acellular areas surrounded by nuclear palisades)<br>• Treatment may involve observation, radiotherapy or surgery. |
| Pilocytic astrocytoma | • The most common primary brain tumour in children<br>• Histology: Rosenthal fibres (corkscrew eosinophilic bundle) |
| Medulloblastoma | • A medulloblastoma is an aggressive paediatric brain tumour that arises within the infratentorial compartment. It spreads through the CSF system. Treatment is surgical resection and chemotherapy.<br>• Histology: Small, blue cells. Rosette pattern of cells with many mitotic figures |
| Ependymoma | • Commonly seen in the 4th ventricle<br>• May cause hydrocephalus<br>• Histology: perivascular pseudorosettes |
| Oligodendroma | • Benign, slow-growing tumour common in the frontal lobes<br>• Histology: Calcifications with 'fried-egg' appearance |

| Type of tumour | Features |
|---|---|
| Haemangioblastoma | • Vascular tumour of the cerebellum<br>• Associated with von Hippel-Lindau syndrome<br>• Histology: foam cells and high vascularity |
| Pituitary adenoma | • Pituitary adenomas are benign tumours of the pituitary gland. They are either secretory (producing a hormone in excess) or non-secretory. They may be divided into microadenomas (smaller than 1cm) or macroadenoma (larger than 1cm).<br>• Patients will present with the consequences of hormone excess (e.g. Cushing's due to ACTH, or acromegaly due to GH) or depletion. Compression of the optic chiasm will cause a bitemporal hemianopia due to the crossing nasal fibers.<br>• Investigation requires a pituitary blood profile and MRI. Treatment can either be hormonal or surgical (e.g. transphenoidal resection). |
| Craniopharyngioma | • Most common paediatric supratentorial tumour<br>• A craniopharyngioma is a solid/cystic tumour of the sellar region that is derived from the remnants of Rathke's pouch. It is common in children, but can present in adults also. It may present with hormonal disturbance, symptoms of hydrocephalus or bitemporal hemianopia.<br>• Histology: Derived from remnants of Rathke pouch<br>• Investigation requires pituitary blood profile and MRI. Treatment is typically surgical with or without postoperative radiotherapy. |



**Meningioma** - MRI showing the typical well-circumscribed appearance. A dural tail can be where the tumour 'connects' to the dura. It is seen in around 65% of meningiomas.



**Glioblastoma multiforme** - CT showing a peripherally enhancing lesion within the left frontal lobe. Note the contrast to the more homogenous meningioma above.

# ACUTE TUBULAR NECROSIS

Acute tubular necrosis (ATN) is the most common cause of acute kidney injury (AKI) seen in clinical practice. Necrosis of renal tubular epithelial cells severely affects the functioning of the kidney. In the early stages ATN is reversible if the cause if removed.

There are two main causes of ATN; ischaemia and nephrotoxins:

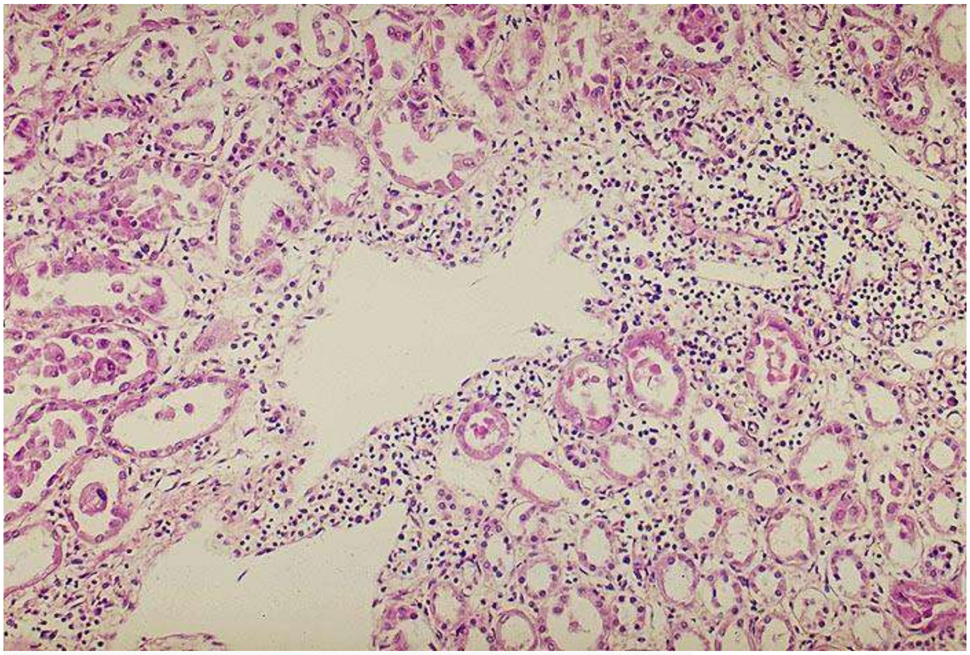
- ischaemia
  - shock
  - sepsis
- nephrotoxins
  - aminoglycosides
  - myoglobin secondary to rhabdomyolysis
  - radiocontrast agents
  - lead

Features

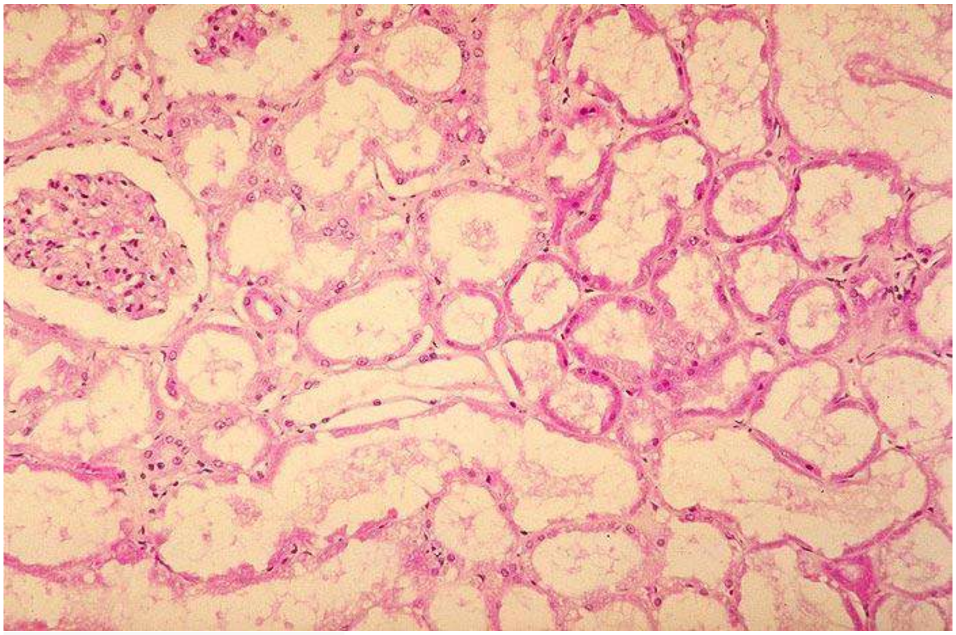
- features of AKI: raised urea, creatinine, potassium
- muddy brown casts in the urine

Histopathological features

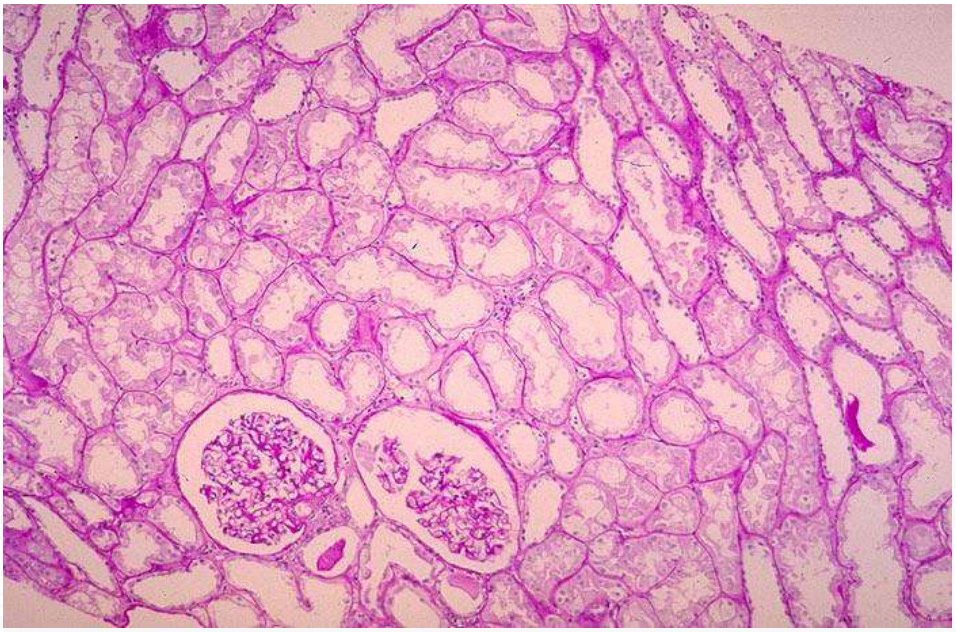
- tubular epithelium necrosis: loss of nuclei and detachment of tubular cells from the basement membrane
- dilatation of the tubules may occur
- necrotic cells obstruct the tubule lumen



Necrotic desquamated epithelial cells inside the tubular lumens



Severe dilatation of the tubules



Section of the renal cortex with diffuse necrosis and tubular dilatation. The glomeruli are normal

Phases of ATN

- oliguric phase
- polyuric phase
- recovery phase

# TEMPORAL ARTERY BIOPSY

- Superficial temporal artery is a terminal branch of the external carotid artery

**Main indication**
- Temporal arteritis

American College of Rheumatology guidelines recommend a temporal artery biopsy if:

- Age of onset older than 50 years
- New-onset headache or localized head pain
- Temporal artery tenderness to palpation or reduced pulsation
- ESR > 50 mm/h

**Histopathology**
- Vessel wall granulomatous arteritis with mononuclear cell infiltrates and giant cell formation

**Procedure**
- Position: supine, head 45 degrees
- USS doppler to locate the superficial temporal artery or palpate
- Local anaesthetic
- Artery within temporoparietal fascia
- Clamp and ligate the vessel
- Cut 3-5cm
- Ligate the remaining ends with absorbable suture
- Close the skin

**Contraindication**

Glucocorticoid therapy > 30 days

**Risks**

Injury to facial or auriculotemporal nerve

# FITNESS TO FLY

The Civil Aviation Authority (CAA) has issued guidelines on air travel for people with medical conditions; please see the link provided.

Cardiovascular disease
- unstable angina, uncontrolled hypertension, uncontrolled cardiac arrhythmia, decompensated heart failure, severe symptomatic valvular disease: should not fly
- uncomplicated myocardial infarction: may fly after 7-10 days
- complicated myocardial infarction: after 4-6 weeks
- coronary artery bypass graft: after 10-14 days
- percutaneous coronary intervention: after 5 days
- stroke: patients are advised to wait 10 days following an event, although if stable may be carried within 3 days of the event

Respiratory disease
- pneumonia: should be 'clinically improved with no residual infection'
- pneumothorax: absolute contraindication, the CAA suggest patients may travel 2 weeks after successful drainage if there is no residual air. The British Thoracic Society used to recommend not travelling by air for a period of 6 weeks but this has now been changed to 1 week post check x-ray

Pregnancy
- most airlines do not allow travel after 36 weeks for a single pregnancy and after 32 weeks for a multiple pregnancy
- most airlines require a certificate after 28 weeks confirming that the pregnancy is progressing normally

Surgery
- travel should be avoided for 10 days following abdominal surgery
- laparoscopic surgery: after 24 hours
- colonoscopy: after 24 hours
- following the application of a plaster cast, the majority of airlines restrict flying for 24 hours on flights of less than 2 hours or 48 hours for longer flights

Haematological disorders
- patients with a haemoglobin of greater than 8 g/dl may travel without problems (assuming there is no coexisting condition such as cardiovascular or respiratory disease)

# BIOSTATISTICS

## STATISTICAL TERMS: DESCRIPTIVE STATISTICS

The table below gives a brief definition of commonly encountered terms:

| Term | Description |
|---|---|
| Mean | The average of a series of observed values |
| Median | The middle value if series of observed values are placed in order |
| Mode | The value that occurs most frequently within a dataset |
| Range | The difference between the largest and smallest observed value |

## CONFIDENCE INTERVAL AND STANDARD ERROR OF THE MEAN

The confidence interval is a common and sometimes misunderstood principle in medical statistics.

- a formal definition may be: *a range of values for a variable of interest constructed so that this range has a specified probability of including the true value of the variable. The specified probability is called the confidence level, and the end points of the confidence interval are called the confidence limits**
- in simpler terms: a range of values within which the true effect of intervention is likely to lie

The likelihood of the true effect lying within the confidence interval is determined by the confidence level. For example a confidence interval at the 95% confidence level means that the confidence interval should contain the true effect of intervention 95% of the time.

**How is the confidence interval calculated?**
The standard error of the mean (SEM) is a measure of the spread expected for the mean of the observations - i.e. how 'accurate' the calculated sample mean is from the true population mean

Key point

- SEM = SD / square root (n)
- where SD = standard deviation and n = sample size
- therefore the SEM gets smaller as the sample size (n) increases

A 95% confidence interval:

- lower limit = mean - (1.96 * SEM)
- upper limit = mean + (1.96 * SEM)

The above formula is a slight simplification:

- if a small sample size is used (e.g. n < 100) then it is important to use a 'Student's T critical value' look-up table to replace 1.96 with a different value
- if a different confidence level is required, e.g. 90% then 1.96 is replaced by a different value. For 90% this would 1.645

Results such as mean value are often presented along with a confidence interval. For example, in a study the mean height in a sample taken from a population is 183cm. You know that the standard error (SE) (the standard deviation of the mean) is 2cm. This gives a 95% confidence interval of 179-187cm (+/- 2 SE).

*Last JM. A dictionary of epidemiology. Oxford: International Journal of Epidemiology, 1988

## VARIANCE

Variance is a measure of the spread of scores away from the mean.

Variance = square of standard deviation

## NORMAL DISTRIBUTION

The normal distribution is also known as the Gaussian distribution or 'bell-shaped' distribution. It describes the spread of many biological and clinical measurements

Properties of the Normal distribution

- symmetrical i.e. Mean = mode = median
- 68.3% of values lie within 1 SD of the mean
- 95.4% of values lie within 2 SD of the mean
- 99.7% of values lie within 3 SD of the mean
- this is often reversed, so that within 1.96 SD of the mean lie 95% of the sample values
- the range of the mean - (1.96 *SD) to the mean + (1.96 * SD) is called the 95% confidence interval, i.e. If a repeat sample of 100 observations are taken from the same group 95 of them would be expected to lie in that range

Standard deviation

- the standard deviation (SD) is a measure of how much dispersion exists from the mean
- SD = square root (variance)

# SKEWED DISTRIBUTIONS

Normal (Gaussian) distributions: mean = median = mode

Positively skewed distribution: mean > median > mode

Negatively skewed distribution mean < median < mode

To remember the above note how they are in alphabetical order, think positive going forward with '>', whilst negative going backwards '<'

# PRE- AND POST- TEST ODDS AND PROBABILITY

**Pre-test probability**

The proportion of people with the target disorder in the population at risk at a specific time (point prevalence) or time interval (period prevalence)

For example, the prevalence of rheumatoid arthritis in the UK is 1%

**Post-test probability**

The proportion of patients with that particular test result who have the target disorder

Post-test probability = post test odds / (1 + post-test odds)

**Pre-test odds**

The odds that the patient has the target disorder before the test is carried out

Pre-test odds = pre-test probability / (1 - pre-test probability)

**Post-test odds**

The odds that the patient has the target disorder after the test is carried out

Post-test odds = pre-test odds x likelihood ratio

where the likelihood ratio for a positive test result = sensitivity / (1 - specificity)

## ODDS AND ODDS RATIO

Odds are a ratio of the number of people who incur a particular outcome to the number of people who do not incur the outcome. The odds ratio may be defined as the ratio of the odds of a particular outcome with experimental treatment and that of control.

**Odds vs. probability**

In contrast, probability is the fraction of times you'd expect to see an event in many trials. When expressed as a single number probability is always between 0 and 1. So, if we take the example of rolling a dice:
- the probability of rolling a six is 1/6 or 0.166666
- the odds of rolling a six is 1/5 or 0.2

Odds ratios are the usual reported measure in case-control studies. It approximates to relative risk if the outcome of interest is rare.

For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

| | Total number of patients | Achieved = 50% pain relief |
|---|---|---|
| **Paracetamol** | 60 | 40 |
| **Placebo** | 90 | 30 |

The odds of achieving significant pain relief with paracetamol = 40 / 20 = 2

The odds of achieving significant pain relief with placebo = 30 / 60 = 0.5

Therefore the odds ratio = 2 / 0.5 = 4

## HAZARD RATIO

The hazard ratio (HR) is similar to relative risk but is used when risk is not constant to time. It is typically used when analysing survival over time

## RELATIVE RISK

**Relative risk (RR)** is the ratio of risk in the experimental group (experimental event rate, EER) to risk in the control group (control event rate, CER). The term relative risk ratio is sometimes used instead of relative risk.

To recap

- EER = rate at which events occur in the experimental group
- CER = rate at which events occur in the control group

For example, if we look at a trial comparing the use of paracetamol for dysmenorrhoea compared to placebo we may get the following results

| | Total number of patients | Experienced significant pain relief |
|---|---|---|
| **Paracetamol** | 100 | 60 |
| **Placebo** | 80 | 20 |

Experimental event rate, EER = 60 / 100 = 0.6

Control event rate, CER = 20 / 80 = 0.25

Therefore the relative risk ratio = EER / CER = 0.6 / 0.25 = 2.4

If the risk ratio is > 1 then the rate of an event (in this case experiencing significant pain relief) is increased compared to controls. It is therefore appropriate to calculate the relative risk increase if necessary (see below).

If the risk ratio is < 1 then the rate of an event is decreased compared to controls. The relative risk reduction should therefore be calculated (see below).

**Relative risk reduction (RRR) or relative risk increase (RRI)** is calculated by dividing the absolute risk change by the control event rate

Using the above data, RRI = (EER - CER) / CER = (0.6 - 0.25) / 0.25 = 1.4 = 140%

## NUMBERS NEEDED TO TREAT AND ABSOLUTE RISK REDUCTION

Numbers needed to treat (NNT) is a measure that indicates how many patients would require an intervention to reduce the expected number of outcomes by one

It is calculated by 1/(Absolute risk reduction) and is rounded to the next highest whole number

Experimental event rate (EER) = (Number who had particular outcome with the intervention) / (Total number who had the intervention)

Control event rate (CER) = (Number who had particular outcome with the control/ (Total number who had the control)

**Absolute risk reduction = CER-EER or EER-CER?**

The absolute risk reduction (ARR) may be calculated by finding the absolute difference between the control event rate (CER) and the experimental event rate (EER). You will often find both versions of the above listed in different sources. In some ways in doesn't matter which you use as you will end up with the same answer but from a technical point of view:

- if the outcome of the study is undesirable then ARR = CER - EER
- if the outcome of the study is desirable then ARR* = EER - CER

*this may be more accurately termed absolute benefit increase, rather than absolute risk reduction

# RELIABILITY AND VALIDITY

Reliability is used in statistics to imply consistency of a measure.

Validity is determined by whether a test accurately measures what it is supposed to measure.

Reliability and validity are independent of each other. A measurement can be valid but not reliable, or reliable but not valid. For example, if a pulse oximeter records the oxygen saturations 5% below the true value every time it is used then from a statistical point of view it is 'reliable' (the value is consistently 5% below the true value) but not 'valid' (as the reported saturations are not an accurate reflection of the true values).

# BIAS

Bias describes the situation in a trial where one outcome is systematically favoured. It should be noted that there is considerable variation in the definitions and classification of bias. The table below lists some of the more common types of bias.

| Type | Description |
|---|---|
| **Selection bias** | Error in assigning individuals to groups leading to differences which may influence the outcome. Subtypes include **sampling bias** where the subjects are not representative of the population. This may be due to **volunteer bias**. An example of volunteer bias would be a study looking at the prevalence of *Chlamydia* in the student population. Students who are at risk of *Chlamydia* may be more, or less, likely to participate in the study. A similar concept is **non-responder bias**. If a survey on dietary habits was sent out in the post to random households it is likely that the people who didn't respond would have poorer diets than those who did.<br>Other examples include |

| Type | Description |
|---|---|
| | • loss to follow up bias<br>• prevalence/incidence bias (Neyman bias): when a study is investigating a condition that is characterised by early fatalities or silent cases. It results from missed cases being omitted from calculations<br>• admission bias (Berkson's bias): cases and controls in a hospital case control study are systematically different from one another because the combination of exposure to risk and occurrence of disease increases the likelihood of being admitted to the hospital<br>• healthy worker effect |
| **Recall bias** | Difference in the accuracy of the recollections retrieved by study participants, possibly due to whether they have disorder or not. E.g. a patient with lung cancer may search their memories more thoroughly for a history of asbestos exposure than someone in the control group. A particular problem in case-control studies. |
| **Publication bias** | Failure to publish results from valid studies, often as they showed a negative or uninteresting result. Important in meta-analyses where studies showing negative results may be excluded. |
| **Work-up bias (verification bias)** | In studies which compare new diagnostic tests with gold standard tests, work-up bias can be an issue. Sometimes clinicians may be reluctant to order the gold standard test unless the new test is positive, as the gold standard test may be invasive (e.g. tissue biopsy). This approach can seriously distort the results of a study, and alter values such as specificity and sensitivity. Sometimes work-up bias cannot be avoided, in these cases it must be adjusted for by the researchers. |
| **Expectation bias (Pygmalion effect)** | Only a problem in non-blinded trials. Observers may subconsciously measure or report data in a way that favours the expected study outcome. |
| **Hawthorne effect** | Describes a group changing it's behaviour due to the knowledge that it is being studied |
| **Late-look bias** | Gathering information at an inappropriate time e.g. studying a fatal disease many years later when some of the patients may have died already |
| **Procedure bias** | Occurs when subjects in different groups receive different treatment |
| **Lead-time bias** | Occurs when two tests for a disease are compared, the new test diagnoses the disease earlier, but there is no effect on the outcome of the disease |

# FUNNEL PLOT

A funnel plot is primarily used to demonstrate the existence of publication bias in meta-analyses. Funnel plots are usually drawn with treatment effects on the horizontal axis and study size on the vertical axis.

Interpretation

- a symmetrical, inverted funnel shape indicates that publication bias is unlikely
- conversely, an asymmetrical funnel indicates a relationship between treatment effect and study size. This indicates either publication bias or a systematic difference between smaller and larger studies ('small study effects')

## CONFOUNDING

In statistics confounding refers to a variable which correlates with other variables within a study leading to spurious results.

For example
- a case-control study looks at whether low-dose aspirin can prevent colorectal cancer
- the proportion of people diagnosed with colorectal who took aspirin is compared to the proportion of people without colorectal cancer who took aspirin
- if the case and control groups are not matched for age then age could be said to be a confounding factor as older people are more likely to take aspirin and also more likely to develop cancer

In another example a study which finds that people who drink coffee are more likely to develop heart disease. The confounding factor in this study is smoking. Smoking is associated with both drinking coffee and heart disease. People who drink coffee are also more likely to smoke. In this case smoking confounds the apparent relationship between coffee and heart disease.

Confounding occurs when there is a non random distribution of risk factors in the populations. Age, sex and social class are common causes of confounding.

In the design stage of an experiment, confounding can be controlled by randomisation which aims to produce an even amount of potential risk factors in two populations.

In the analysis stage of an experiment, confounding can be controlled for by stratification.

## CORRELATION AND LINEAR REGRESSION

The terms correlation and regression are related but are not synonymous. Correlation is used to test for association between variables (e.g. whether salary and IQ are related). Once correlation between two variables has been shown regression can be used to predict values of other dependent variables from independent variables. Regression is not used unless two variables have firstly been shown to correlate.

**Correlation**

The degree of correlation is summarised by the correlation coefficient (r). This indicates how closely the points lie to a line drawn through the plotted data. In parametric data this is called Pearson's correlation coefficient and can take any value between -1 to +1.

For example
- r = 1 - strong positive correlation (e.g. systolic blood pressure always increases with age)
- r = 0 - no correlation (e.g. there is no correlation between systolic blood pressure and age)
- r = - 1 - strong negative correlation (e.g. systolic blood pressure always decreases with age)

Whilst correlation coefficients give information about how one variable may increase or decrease as another variable increases they do not give information about how much the variable will change. They also do not provide information on cause and effect.

Correlation is summarised when using parametric variables by Pearson's correlation coefficient (represented by a small r). In the situation of non parametric variables, Spearman's correlation coefficient is used. Spearman's correlation coefficient is usually represented by the Greek letter p (rho), or by rs.

In the case of dichotomous variables logistic regression is used. Linear (or simple linear) regression is used when looking for association between two continuous variables, and multiple regression is used when looking for association between more than two continuous variables.

**Linear regression**

In contrast to the correlation coefficient, linear regression may be used to predict how much one variable changes when a second variable is changed. A regression equation may be formed, $y = a + bx$, where
- y = the variable being calculated
- a = the intercept value, when x = 0
- b = the slope of the line or regression coefficient. Simply put, how much y changes for a given change in x
- x = the second variable

# SCREENING TEST STATISTICS

Patients and doctors need to know if a disease or condition is present or absent. Tests can be used to help us decide. Tests generally guide us by indicating how likely it is that the patient has the condition.

In order to interpret test results we need to have a working knowledge of the statistics used to describe them.

Contingency tables (also known as 2 * 2 tables, see below) are used to illustrate and calculate test statistics such as sensitivity. It would be unusual for a medical exam not to feature a question based around screening test statistics. Commit the following table to memory and spend time practising using it as you will be expected to make calculations using it in your exam.

TP = true positive; FP = false positive; TN = true negative; FN = false negative

| | Disease present | Disease absent |
|---|---|---|
| **Test positive** | TP | FP |
| **Test negative** | FN | TN |

The table below lists the main statistical terms used in relation to screening tests:

| Measure | Formula | Plain english |
|---|---|---|
| **Sensitivity** | TP / (TP + FN ) | Proportion of patients with the condition who have a positive test result |
| **Specificity** | TN / (TN + FP) | Proportion of patients without the condition who have a negative test result |
| **Positive predictive value** | TP / (TP + FP) | The chance that the patient has the condition if the diagnostic test is positive |
| **Negative predictive value** | TN / (TN + FN) | The chance that the patient does not have the condition if the diagnostic test is negative |
| **Likelihood ratio for a positive test result** | sensitivity / (1 - specificity) | How much the odds of the disease increase when a test is positive |
| **Likelihood ratio for a negative test result** | (1 - sensitivity) / specificity | How much the odds of the disease decrease when a test is negative |

Positive and negative predictive values are prevalence dependent. Likelihood ratios are not prevalence dependent.

**Precision**

The precision quantifies a tests ability to produce the same measurements with repeated tests.

# DATA TYPES

| Data type | Description |
|---|---|
| Nominal | Observed values can be put into set categories which have no particular order or hierarchy. You can count but not order or measure nominal data (for example birthplace) |
| Ordinal | Observed values can be put into set categories which themselves can be ordered (for example NYHA classification of heart failure symptoms) |
| Discrete | Observed values are confined to a certain values, usually a finite number of whole numbers (for example the number of asthma exacerbations in a year) |

| Data type | Description |
|---|---|
| Continuous | Data can take any value with certain range (for example weight) |
| Binomial | Data may take one of two values (for example gender) |
| Interval | A measurement where the difference between two values is meaningful, such that equal differences between values correspond to real differences between the quantities that the scale measures (for example temperature) |

# CLINICAL TRIAL: PHASES

Clinical trials are commonly classified into 4 phases;

| Phase | Goal | Notes |
|---|---|---|
| I | Determines pharmacokinetics and pharmacodynamics and side-effects prior to larger studies | Conducted on healthy volunteers |
| II | Assess efficacy + dosage | Involves small number of patients affected by particular disease<br>May be subdivided into<br>• IIa - assesses optimal dosing<br>• IIb - assesses efficacy |
| III | Assess effectiveness | Typically involves 100-1000's of people, often as part of a randomised controlled trial, comparing new treatment with established treatments |
| IV | Postmarketing surveillance | Monitors for long-term effectiveness and side-effects |

# STUDY DESIGN

The following table highlights the main features of the main types of study:

| Study type | Key features |
|---|---|
| **Randomised controlled trial** | Participants randomly allocated to intervention or control group (e.g. standard treatment or placebo)<br>Practical or ethical problems may limit use |
| **Cohort study** | Observational and prospective. Two (or more) are selected according to their exposure to a particular agent (e.g. medicine, toxin) and followed up to see how many develop a disease or other outcome. |

| Study type | Key features |
|---|---|
| | The usual outcome measure is the relative risk.<br>Examples include Framingham Heart Study |
| **Case-control study** | Observational and retrospective. Patients with a particular condition (cases) are identified and matched with controls. Data is then collected on past exposure to a possible causal agent for the condition.<br>The usual outcome measure is the odds ratio.<br>Inexpensive, produce quick results<br>Useful for studying rare conditions<br>Prone to confounding |
| **Cross-sectional survey** | Provide a 'snapshot', sometimes called prevalence studies<br>Provide weak evidence of cause and effect |

# STUDY DESIGN: EVIDENCE AND RECOMMENDATIONS

Levels of evidence
Ia - evidence from meta-analysis of randomised controlled trials
Ib - evidence from at least one randomised controlled trial
IIa - evidence from at least one well designed controlled trial which is not randomised
IIb - evidence from at least one well designed experimental trial
III - evidence from case, correlation and comparative studies
IV - evidence from a panel of experts

Grading of recommendation
Grade A - based on evidence from at least one randomised controlled trial (i.e. Ia or Ib)
Grade B - based on evidence from non-randomised controlled trials (i.e. IIa, IIb or III)
Grade C - based on evidence from a panel of experts (i.e. IV)

# STUDY DESIGN: NEW DRUGS

When a new drug is launched there are a number of options available in terms of study design. One option is a placebo controlled trial. Whilst this may provide robust evidence it may be considered unethical if established treatments are available and it also does not provide a comparison with standard treatments.

If a drug is therefore to be compared to an existing treatment a statistician will need to decide whether the trial is intended to show superiority, equivalence or non-inferiority:

- superiority: whilst this may seem the natural aim of a trial one problem is the large sample size needed to show a significant benefit over an existing treatment
- equivalence: an equivalence margin is defined (-delta to +delta) on a specified outcome. If the confidence interval of the difference between the two drugs lies within the equivalence margin then the drugs may be assumed to have a similar effect
- non-inferiority: similar to equivalence trials, but only the lower confidence interval needs to lie within the equivalence margin (i.e. -delta). Small sample sizes are needed for these trials. Once a drug has been shown to be non-inferior large studies may be performed to show superiority

It should be remembered that drug companies may not necessarily want to show superiority over an existing product. If it can be demonstrated that their product is equivalent or even non-inferior then they may compete on price or convenience.

# SIGNIFICANCE TESTS

A null hypothesis (H0) states that two treatments are equally effective (and is hence negatively phrased). A significance test uses the sample data to assess how likely the null hypothesis is to be correct.

For example:

- 'there is no difference in the prevalence of colorectal cancer in patients taking low-dose aspirin compared to those who are not'

The alternative hypothesis (H1) is the opposite of the null hypothesis, i.e. There is a difference between the two treatments

The **p value** is the probability of obtaining a result by chance at least as extreme as the one that was actually observed, assuming that the null hypothesis is true. It is therefore equal to the chance of making a type I error (see below).

Two types of errors may occur when testing the null hypothesis

- type I: the null hypothesis is rejected when it is true - i.e. Showing a difference between two groups when it doesn't exist, a false positive. This is determined against a preset significance level (termed alpha). As the significance level is determined in advance the chance of making a type I error is not affected by sample size. It is however increased if the number of end-points are increased. For example if a study has 20 end-points it is likely one of these will be reached, just by chance.
- type II: the null hypothesis is accepted when it is false - i.e. Failing to spot a difference when one really exists, a false negative. The probability of making a type II error is termed beta. It is determined by both sample size and alpha

| | **Study accepts $H_0$** | **Study rejects $H_0$** |
|---|---|---|
| **Reality $H_0$** | | Type 1 error (alpha) |
| **Reality $H_1$** | Type 2 error (beta) | Power (1 - beta) |

The power of a study is the probability of (correctly) rejecting the null hypothesis when it is false, i.e. the probability of detecting a statistically significant difference

- power = 1 - the probability of a type II error
- power can be increased by increasing the sample size

# SIGNIFICANCE TESTS: TYPES

The type of significance test used depends on whether the data is parametric (something which can be measured, usually normally distributed) or non-parametric

Parametric tests

- Student's t-test - paired or unpaired*
- Pearson's product-moment coefficient - correlation

Non-parametric tests

- Mann-Whitney U test - unpaired data
- Wilcoxon signed-rank test - compares two sets of observations on a single sample
- chi-squared test - used to compare proportions or percentages
- Spearman, Kendall rank - correlation

*paired data refers to data obtained from a single group of patients, e.g. Measurement before and after an intervention. Unpaired data comes from two different groups of patients, e.g. Comparing response to different interventions in two groups

## INTENTION TO TREAT ANALYSIS

Intention to treat analysis is a method of analysis for randomized controlled trials in which all patients randomly assigned to one of the treatments are analysed together, regardless of whether or not they completed or received that treatment

Intention to treat analysis is done to avoid the effects of crossover and drop-out, which may affect the randomization to the treatment groups

## SCREENING: WILSON AND JUNGER CRITERIA

1. The condition should be an important public health problem

2. There should be an acceptable treatment for patients with recognised disease

3. Facilities for diagnosis and treatment should be available

4. There should be a recognised latent or early symptomatic stage

5. The natural history of the condition, including its development from latent to declared disease should be adequately understood

6. There should be a suitable test or examination

7. The test or examination should be acceptable to the population

8. There should be agreed policy on whom to treat

9. The cost of case-finding (including diagnosis and subsequent treatment of patients) should be economically balanced in relation to the possible expenditure as a whole

10. Case-finding should be a continuous process and not a 'once and for all' project

## INCIDENCE AND PREVALENCE

These two terms are used to describe the frequency of a condition in a population.

The **incidence** is the number of new cases per population in a given time period.

For example, if condition X has caused 40 new cases over the past 12 months per 1,000 of the population the annual incidence is 0.04 or 4%.

The **prevalence** is the total number of cases per population at a particular point in time.

For example, imagine a questionnaire is sent to 2,500 adults asking them how much they weigh. If from this sample population of 500 of the adults were obese then the prevalence of obesity would be 0.2 or 20%.

Relationship
- prevalence = incidence * duration of condition
- in chronic diseases the prevalence is much greater than the incidence
- in acute diseases the prevalence and incidence are similar. For conditions such as the common cold the incidence may be greater than the prevalence

# GMC GUIDANCE: CONFIDENTIALITY

We will not try to replicate the extensive guidance given by the General Medical Council here. There is a link available for more detailed information.

# PATIENTS WHO REFUSE TREATMENT

Many patients who are admitted to hospital, or treated in the community, lack capacity. In the vast majority of cases, these patients do not refuse treatment that is given that is deemed to be in their best interest. The problem arises when patients who lack (or are suspected of lacking) capacity refuse treatment.

There are 3 main frameworks that are used in this scenario:

- common law: used to treat patients in **emergency scenarios**
- Mental Capacity Act: (MCA) used in patients who require treatment for **physical disorders** that affect brain function. Remember this may be delirium secondary to sepsis or a primary brain disorder such as dementia
- Mental Health Act (MHA): used in patients who require treatment for **mental disorders**. For patients already admitted to hospital, a section 5(2) is used if there is not the time for a more formal section 2 or 3. A typical scenario would be a patient who has a mental health disorder attempting to discharge themselves, when it is thought this may result in harm

An excellent, more in-depth review can be found in the BMJ 'When and how to treat patients who refuse treatment'. BMJ 2014;348;g2043

# PASSMEDICINE NOTES PHARMACOLOGY

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# PHARMACOKINETICS: METABOLISM

Drug metabolism usually involves two types of biochemical reactions - phase I and phase II reactions
- phase I reactions: oxidation, reduction, hydrolysis. Mainly performed by the P450 enzymes but some drugs are metabolised by specific enzymes, for example alcohol dehydrogenase and xanthine oxidase. Products of phase I reactions are typically more active and potentially toxic
- phase II reactions: conjugation. Products are typically inactive and excreted in urine or bile. Glucuronyl, acetyl, methyl, sulphate and other groups are typically involved

The majority of phase I and phase II reactions take place in the liver

**First-pass metabolism**
This is a phenomenon where the concentration of a drug is greatly reduced before it reaches the systemic circulation due to hepatic metabolism. As a consequence much larger doses are need orally than if given by other routes. This effect is seen in many drugs, including:
- aspirin
- isosorbide dinitrate
- glyceryl trinitrate
- lignocaine
- propranolol
- verapamil
- isoprenaline
- testosterone
- hydrocortisone

Questions concerning zero-order kinetics and acetylator status are also common in the exam

**Zero-order kinetics**
Zero-order kinetics describes metabolism which is independent of the concentration of the reactant. This is due to metabolic pathways becoming saturated resulting in a constant amount of drug being eliminated per unit time. This explains why people may fail a breathalyser test in the morning if they have been drinking the night before

Drugs exhibiting zero-order kinetics
- phenytoin
- salicylates (e.g. high-dose aspirin)
- heparin
- ethanol

**Acetylator status**
50% of the UK population are deficient in hepatic N-acetyltransferase

Drugs affected by acetylator status

- isoniazid
- procainamide
- hydralazine
- dapsone
- sulfasalazine

## PHARMACOKINETICS: EXCRETION

Clearance

- majority of drugs exhibit 'first-order' elimination kinetics i.e. the rate of drug elimination is proportional to drug concentration
- certain drugs exhibit zero-order kinetics where the rate of excretion is constant despite changes in plasma concentration, this is due to saturation of the metabolic process
- examples of drugs exhibiting zero-order kinetics include phenytoin and salicylates

## DRUGS ACTING ON COMMON RECEPTORS

The table below lists the common receptors and gives examples of both agonists and antagonists. It is not comprehensive and is intended to give examples of each.

| Receptor | Agonist | Antagonist |
|---|---|---|
| Alpha | Alpha-1: Decongestants (e.g. phenylephrine/oxymetazoline)<br>Alpha-2: Glaucoma (e.g. topical brimonidine) | Benign prostatic hyperplasia (e.g. tamsulosin)<br>Hypertension (e.g. doxazosin) |
| Beta-1 | Inotropes (e.g. dobutamine) | Non-selective & selective beta-blockers (e.g. atenolol, bisoprolol) |
| Beta-2 | Bronchodilators (e.g. salbutamol) | Non-selective beta-blockers (e.g. propranolol, labetalol) |
| Dopamine | Parkinson's disease (e.g. ropinirole)<br>Prolactinoma | Schizophrenia (antipsychotics e.g. haloperidol)<br>Anti-emetics (e.g. metoclopramide/domperidone) |
| GABA | Benzodiazepines<br>Baclofen | Flumazenil |
| Histamine-1 | | Antihistamines (e.g. loratadine) |
| Histamine-2 | | Antacids (e.g. ranitidine) |
| Muscarinic | Glaucoma (e.g. pilocarpine) | Atropine (e.g. for bradycardia)<br>Bronchodilator (e.g. ipratropium bromide, |

| Receptor | Agonist | Antagonist |
|---|---|---|
| | | tiotropium)<br>Urge incontinence (e.g. oxybutynin) |
| Nicotinic | Nicotine<br>Varenicline (used for smoking cessation)<br>Depolarising muscle relaxant (e.g. suxamethonium) | Non-depolarising muscle relaxants (e.g. atracurium) |
| Oxytocin | Inducing labour (e.g. Syntocinon) | Tocolysis (e.g. atosiban) |
| Serotonin | Triptans (for acute migraine, e.g. zolmitriptan) | Anti-emetics (e.g. ondansetron) |

# P450 ENZYME SYSTEM

Induction usually requires prolonged exposure to the inducing drug, as opposed to P450 inhibitors, where effects are often seen rapidly

Inducers of the P450 system include
- antiepileptics: phenytoin, carbamazepine
- barbiturates: phenobarbitone
- rifampicin
- St John's Wort
- chronic alcohol intake
- griseofulvin
- smoking (affects CYP1A2, reason why smokers require more aminophylline)

Inhibitors of the P450 system include
- antibiotics: ciprofloxacin, erythromycin
- isoniazid
- cimetidine,omeprazole
- amiodarone
- allopurinol
- imidazoles: ketoconazole, fluconazole
- SSRIs: fluoxetine, sertraline
- ritonavir
- sodium valproate
- acute alcohol intake
- quinupristin

# ADRENOCEPTORS

Alpha-1
- vasoconstriction
- relaxation of GI smooth muscle
- salivary secretion
- hepatic glycogenolysis

Alpha-2
- mainly presynaptic: inhibition of transmitter release (inc NA, Ach from autonomic nerves)
- inhibits insulin
- platelet aggregation

Beta-1
- mainly located in the heart
- increase heart rate + force

Beta-2
- vasodilation
- bronchodilation
- relaxation of GI smooth muscle

Beta-3
- lipolysis

Pathways
- all are G-protein coupled
- alpha-1:activate phospholipase C → IP3 → DAG
- alpha-2: inhibit adenylate cyclase
- beta-1: stimulate adenylate cyclase
- beta-2: stimulate adenylate cyclase
- beta-3: stimulate adenylate cyclase

# ADRENOCEPTOR AGONISTS

Alpha-1 agonists
- phenylephrine

Alpha-2 agonists
- clonidine

Beta-1 agonists
- dobutamine

Beta-2 agonists
- salbutamol

Beta-3 agonists
- being developed, may have a role in preventing obesity (stimulation causes lipolysis)

# ADRENOCEPTOR ANTAGONISTS

Alpha antagonists
- alpha-1: doxazosin
- alpha-1a: tamsulosin - acts mainly on urogenital tract
- alpha-2: yohimbine
- non-selective: phenoxybenzamine (previously used in peripheral arterial disease)

Beta antagonists
- beta-1: atenolol
- non-selective: propranolol

Carvedilol and labetalol are mixed alpha and beta antagonists

# DOPAMINE RECEPTOR AGONISTS

Indications
- Parkinson's disease
- prolactinoma/galactorrhoea
- cyclical breast disease
- acromegaly

Currently accepted practice in the management of patients with Parkinson's disease is to delay treatment until the onset of disabling symptoms and then to introduce a dopamine receptor agonist. If the patient is elderly, L-dopa is sometimes used as an initial treatment

Overview
- e.g. bromocriptine, ropinirole, cabergoline, apomorphine
- ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide*) have been associated with pulmonary, retroperitoneal and cardiac fibrosis. The Committee on Safety of

Medicines advice that an ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored

Adverse effects
- nausea/vomiting
- postural hypotension
- hallucinations
- daytime somnolence

*pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of valvular dysfunction

# DRUGS WHICH ACT ON SEROTONIN RECEPTORS

Below is a summary of drugs which are known to act via modulation of the serotonin (5-HT) system. It should be noted that 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis

Agonists
- sumatriptan is a 5-HT1D receptor agonist which is used in the acute treatment of migraine
- ergotamine is a partial agonist of 5-HT1 receptors

Antagonists
- pizotifen is a 5-HT2 receptor antagonist used in the prophylaxis of migraine attacks. Methysergide is another antagonist of the 5-HT2 receptor but is rarely used due to the risk of retroperitoneal fibrosis
- cyproheptadine is a 5-HT2 receptor antagonist which is used to control diarrhoea in patients with carcinoid syndrome
- ondansetron is a 5-HT3 receptor antagonist and is used as an antiemetic

# ANTIARRHYTHMICS: VAUGHAN WILLIAMS CLASSIFICATION

The Vaughan Williams classification of antiarrhythmics is still widely used although it should be noted that a number of common drugs are not included in the classification e.g. adenosine, atropine, digoxin and magnesium

AP = action potential

| Class | Examples | Mechanism of action | Notes |
|---|---|---|---|
| Ia | Quinidine<br>Procainamide<br>Disopyramide | Block sodium channels<br>Increases AP duration | Quinidine toxicity causes cinchonism (headache, tinnitus, thrombocytopaenia)<br>Procainamide may cause drug-induced lupus |
| Ib | Lidocaine<br>Mexiletine<br>Tocainide | Block sodium channels<br>Decreases AP duration | |
| Ic | Flecainide<br>Encainide<br>Propafenone | Block sodium channels<br>No effect on AP duration | |
| II | Propranolol<br>Atenolol<br>Bisoprolol<br>Metoprolol | Beta-adrenoceptor antagonists | |
| III | Amiodarone<br>Sotalol<br>Ibutilide<br>Bretylium | Block potassium channels | |
| IV | Verapamil<br>Diltiazem | Calcium channel blockers | |

# FLECAINIDE

Flecainide is a Vaughan Williams class 1c antiarrhythmic. It slows conduction of the action potential by acting as a potent sodium channel blocker (specifically the Nav1.5 sodium channels). This may be reflected by widening of the QRS complex and prolongation of the PR interval.

The Cardiac Arrhythmia Suppression Trial (CAST, 1989) investigated the use of agents to treat asymptomatic or mildly symptomatic premature ventricular complexes (PVCs) post myocardial infarction. The hypothesis was that this would reduce deaths from ventricular arrhythmias. Flecainide was actually shown to increase mortality post-myocardial infarction and is, therefore, contraindicated in this situation.

Indications

- atrial fibrillation
- SVT associated with accessory pathway e.g. Wolf-Parkinson-White syndrome

Contraindications

- post myocardial infarction
- structural heart disease: e.g. heart failure
- sinus node dysfunction; second-degree or greater AV block
- atrial flutter

Adverse effects

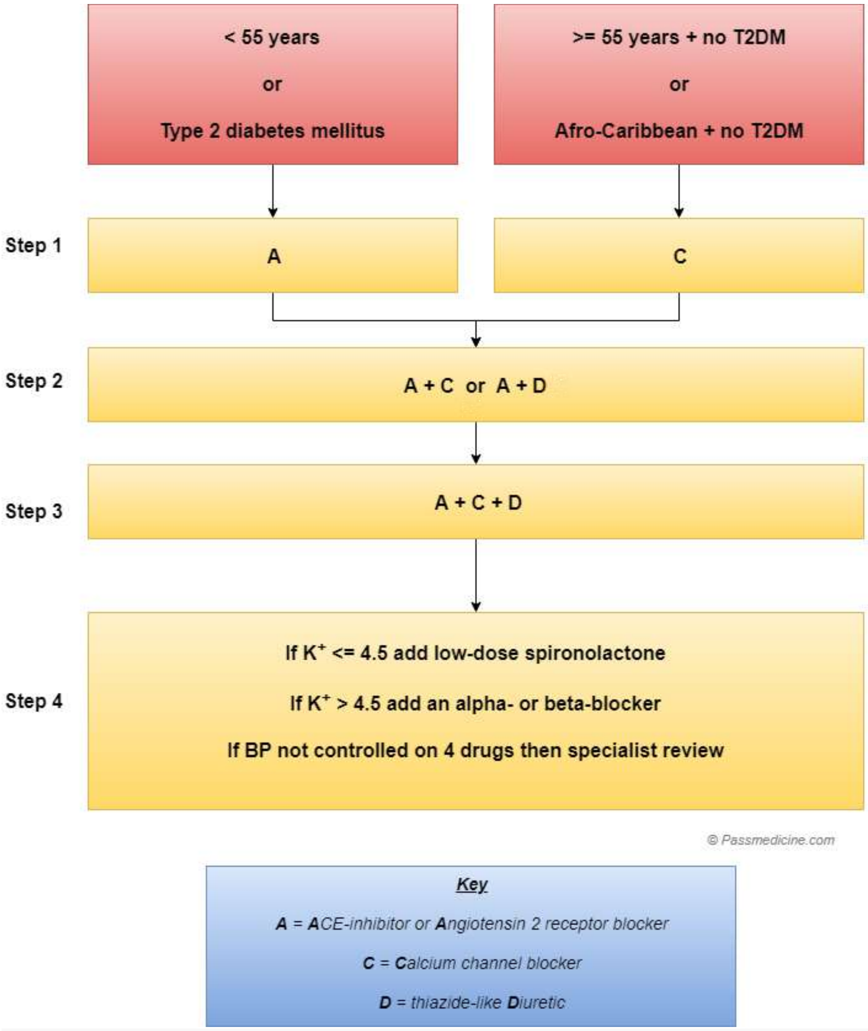
- negatively inotropic
- bradycardia
- proarrhythmic
- oral paraesthesia
- visual disturbances

# CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are primarily used in the management of cardiovascular disease. Voltage-gated calcium channels are present in myocardial cells, cells of the conduction system and those of the vascular smooth muscle. The various types of calcium channel blockers have varying effects on these three areas and it is therefore important to differentiate their uses and actions.

| Examples | Indications & notes | Side-effects and cautions |
|---|---|---|
| **Verapamil** | Angina, hypertension, arrhythmias<br>Highly negatively inotropic<br>Should not be given with beta-blockers as may cause heart block | Heart failure, constipation, hypotension, bradycardia, flushing |
| **Diltiazem** | Angina, hypertension<br>Less negatively inotropic than verapamil but caution should still be exercised when patients have heart failure or are taking beta-blockers | Hypotension, bradycardia, heart failure, ankle swelling |
| **Nifedipine, amlodipine,** | Hypertension, angina, Raynaud's | Flushing, headache, ankle swelling |

| Examples | Indications & notes | Side-effects and cautions |
|---|---|---|
| **felodipine (dihydropyridines)** | Affects the peripheral vascular smooth muscle more than the myocardium and therefore do not result in worsening of heart failure but may therefore cause ankle swelling | |


< 55 years
or
Type 2 diabetes mellitus
>= 55 years + no T2DM
or
Afro-Caribbean + no T2DM
Step 1
A
C
Step 2
A + C or A + D
Step 3
A + C + D
Step 4
If K$^+$ <= 4.5 add low-dose spironolactone
If K$^+$ > 4.5 add an alpha- or beta-blocker
If BP not controlled on 4 drugs then specialist review
© Passmedicine.com
Key
A = ACE-inhibitor or Angiotensin 2 receptor blocker
C = Calcium channel blocker
D = thiazide-like Diuretic

Flow chart showing the management of hypertension as per current NICE guidelines

# DIGOXIN AND DIGOXIN TOXICITY

Digoxin is a cardiac glycoside now mainly used for rate control in the management of atrial fibrillation. As it has positive inotropic properties it is sometimes used for improving symptoms (but not mortality) in patients with heart failure.

Mechanism of action
- decreases conduction through the atrioventricular node which slows the ventricular rate in atrial fibrillation and flutter
- increases the force of cardiac muscle contraction due to inhibition of the Na+/K+ ATPase pump. Also stimulates vagus nerve
- digoxin has a narrow therapeutic index

Monitoring
- digoxin level is not monitored routinely, except in suspected toxicity
- if toxicity is suspected, digoxin concentrations should be measured within 8 to 12 hours of the last dose

**Digoxin toxicity**
Plasma concentration alone does not determine whether a patient has developed digoxin toxicity. Toxicity may occur even when the concentration is within the therapeutic range. The BNF advises that the likelihood of toxicity increases progressively from 1.5 to 3 mcg/l.

Features
- generally unwell, lethargy, nausea & vomiting, anorexia, confusion, yellow-green vision
- arrhythmias (e.g. AV block, bradycardia)
- gynaecomastia

Precipitating factors
- classically: hypokalaemia
  - digoxin normally binds to the ATPase pump on the same site as potassium. Hypokalaemia → digoxin more easily bind to the ATPase pump → increased inhibitory effects
- increasing age
- renal failure
- myocardial ischaemia
- hypomagnesaemia, hypercalcaemia, hypernatraemia, acidosis
- hypoalbuminaemia
- hypothermia
- hypothyroidism
- drugs: amiodarone, quinidine, verapamil, diltiazem, spironolactone (competes for secretion in distal convoluted tubule therefore reduce excretion), ciclosporin. Also drugs which cause hypokalaemia e.g. thiazides and loop diuretics

Management

- Digibind
- correct arrhythmias
- monitor potassium

# METFORMIN

Metformin is a biguanide used mainly in the treatment of type 2 diabetes mellitus. It has a number of actions which improves glucose tolerance (see below). Unlike sulphonylureas it does not cause hypoglycaemia and weight gain and is therefore first-line, particularly if the patient is overweight. Metformin is also used in polycystic ovarian syndrome and non-alcoholic fatty liver disease

Mechanism of action

- acts by activation of the AMP-activated protein kinase (AMPK)
- increases insulin sensitivity
- decreases hepatic gluconeogenesis
- may also reduce gastrointestinal absorption of carbohydrates

Adverse effects

- gastrointestinal upsets are common (nausea, anorexia, diarrhoea), intolerable in 20%
- reduced vitamin B12 absorption - rarely a clinical problem
- lactic acidosis* with severe liver disease or renal failure

Contraindications

- chronic kidney disease: NICE recommend that the dose should be reviewed if the creatinine is > 130 µmol/l (or eGFR < 45 ml/min) and stopped if the creatinine is > 150 µmol/l (or eGFR < 30 ml/min)
- metformin may cause lactic acidosis if taken during a period where there is tissue hypoxia. Examples include a recent myocardial infarction, sepsis, acute kidney injury and severe dehydration
- iodine-containing x-ray contrast media: examples include peripheral arterial angiography, coronary angiography, intravenous pyelography (IVP); there is an increasing risk of provoking renal impairment due to contrast nephropathy; metformin should be discontinued on the day of the procedure and for 48 hours thereafter
- alcohol abuse is a relative contraindication

Starting metformin

- metformin should be titrated up slowly to reduce the incidence of gastrointestinal side-effects
- if patients develop unacceptable side-effects then modified-release metformin should be considered

*it is now increasingly recognised that lactic acidosis secondary to metformin is rare, although it remains important in the context of exams

# HYPERLIPIDAEMIA: MECHANISM OF ACTION AND ADVERSE EFFECTS

The following table compares the side-effects of drugs used in hyperlipidaemia:

| Drugs | Mechanism of action | Adverse effects |
|---|---|---|
| Statins | HMG CoA reductase inhibitors | Myositis, deranged LFTs |
| Ezetimibe | Decreases cholesterol absorption in the small intestine | Headache |
| Nicotinic acid | Decreases hepatic VLDL secretion | Flushing, myositis |
| Fibrates | Agonist of PPAR-alpha therefore increases lipoprotein lipase expression | Myositis, pruritus, cholestasis |
| Cholestyramine | Decreases bile acid reabsorption in the small intestine, upregulating the amount of cholesterol that is converted to bile acid | GI side-effects |

# POTASSIUM-SPARING DIURETICS

Potassium-sparing diuretics may be divided into the epithelial sodium channel blockers (amiloride and triamterene) and aldosterone antagonists (spironolactone and eplerenone).

**Amiloride** is a weak diuretic which blocks the epithelial sodium channel in the distal convoluted tubule.

Usually given with thiazides or loop diuretics as an alternative to potassium supplementation.

**Spironolactone** is an aldosterone antagonist which acts act in the distal convoluted tubule.

Indications
- ascites: patients with cirrhosis develop a secondary hyperaldosteronism. Relatively large doses such as 100 or 200mg are often used
- heart failure
- nephrotic syndrome
- Conn's syndrome

# PRESCRIBING IN PATIENTS WITH HEART FAILURE

The following medications may exacerbate heart failure:

- thiazolidinediones
  - pioglitazone is contraindicated as it causes fluid retention
- verapamil
  - negative inotropic effect
- NSAIDs/glucocorticoids
  - should be used with caution as they cause fluid retention
  - low-dose aspirin is an exception - many patients will have coexistent cardiovascular disease and the benefits of taking aspirin easily outweigh the risks
- class I antiarrhythmics
  - flecainide (negative inotropic and proarrhythmic effect)

# PRESCRIBING IN PATIENTS WITH RENAL FAILURE

Questions regarding which drugs to avoid in renal failure are common

Drugs to avoid in renal failure

- antibiotics: tetracycline, nitrofurantoin
- NSAIDs
- lithium
- metformin

Drugs likely to accumulate in chronic kidney disease - need dose adjustment

- most antibiotics including penicillins, cephalosporins, vancomycin, gentamicin, streptomycin
- digoxin, atenolol
- methotrexate
- sulphonylureas
- furosemide
- opioids

Drugs relatively safe - can sometimes use normal dose depending on the degree of chronic kidney disease

- antibiotics: erythromycin, rifampicin
- diazepam
- warfarin

# PRESCRIBING IN PREGNANT PATIENTS

Very few drugs are known to be completely safe in pregnancy. The list below largely comprises of those known to be harmful. Some countries have developed a grading system - see the link.

Antibiotics
- tetracyclines
- aminoglycosides
- sulphonamides and trimethoprim
- quinolones: the BNF advises to avoid due to arthropathy in some animal studies

Other drugs
- ACE inhibitors, angiotensin II receptor antagonists
- statins
- warfarin
- sulfonylureas
- retinoids (including topical)
- cytotoxic agents

The majority of antiepileptics including valproate, carbamazepine and phenytoin are known to be potentially harmful. The decision to stop such treatments however is difficult as uncontrolled epilepsy is also a risk

# TERATOGENS

The following table includes some of the drugs and medical conditions that may harm a developing fetus:

| Drug/condition | Effect |
|---|---|
| ACE inhibitors | Renal dysgenesis<br>Craniofacial abnormalities |
| Alcohol | Craniofacial abnormalities |
| Aminoglycosides | Ototoxicity |
| Carbamazepine | Neural tube defects<br>Craniofacial abnormalities |
| Chloramphenicol | 'Grey baby' syndrome |
| Cocaine | Intrauterine growth retardation<br>Preterm labour |
| Diethylstilbesterol | Vaginal clear cell adenocarcinoma |
| Lithium | Ebstein's anomaly (atrialized right ventricle) |
| Maternal diabetes mellitus | Macrosomia<br>Neural tube defects<br>Polyhydramnios |

| Drug/condition | Effect |
|---|---|
| | Preterm labour<br>Caudal regression syndrome |
| Smoking | Preterm labour<br>Intrauterine growth retardation |
| Tetracyclines | Discoloured teeth |
| Thalidomide | Limb reduction defects |
| Valproate | Neural tube defects<br>Craniofacial abnormalities |
| Warfarin | Craniofacial abnormalities |

# ANTIBIOTICS: GROSS MECHANISM OF ACTION

The diagram and list below summarises the gross mechanism of action of the commonly used antibiotics. More detailed descriptions are found elsewhere on the site.

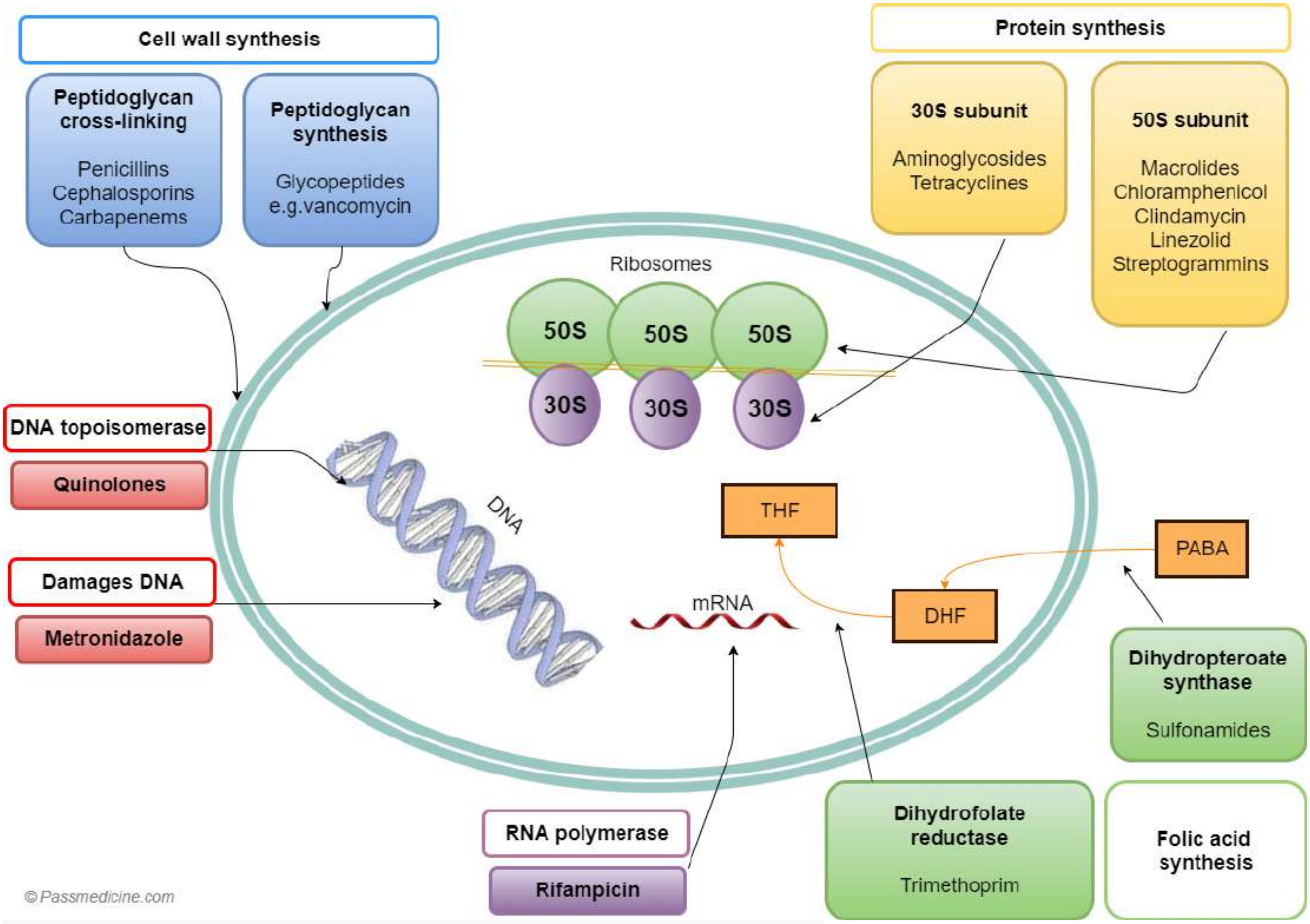

Cell wall synthesis
Peptidoglycan cross-linking
Penicillins
Cephalosporins
Carbapenems
Peptidoglycan synthesis
Glycopeptides e.g.vancomycin
Protein synthesis
30S subunit
Aminoglycosides
Tetracyclines
50S subunit
Macrolides
Chloramphenicol
Clindamycin
Linezolid
Streptogrammins
Ribosomes
50S
50S
50S
30S
30S
30S
DNA topoisomerase
Quinolones
DNA
Damages DNA
Metronidazole
THF
PABA
DHF
mRNA
Dihydropteroate synthase
Sulfonamides
RNA polymerase
Rifampicin
Dihydrofolate reductase
Trimethoprim
Folic acid synthesis
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Diagram showing the gross mechanism of action of the commonly used antibiotics

Inhibits cell wall formation
- peptidoglycan cross-linking: penicillins, cephalosporins, carbopenems
- peptidoglycan synthesis: glycopeptides (e.g. vancomycin)

Inhibits protein synthesis (by acting on the ribosome)
- 50S subunit: macrolides, chloramphenicol, clindamycin, linezolid, streptogrammins
- 30S subunit: aminoglycosides, tetracyclines

Inhibits DNA synthesis
- quinolones (e.g. ciprofloxacin)

Damages DNA
- metronidazole

Inhibits folic acid formation
- sulphonamides
- trimethoprim

Inhibits RNA synthesis
- rifampicin

## GENTAMICIN

Gentamicin is a type of aminoglycoside antibiotic. It is poorly lipid-soluble and is therefore given parentally (e.g. for infective endocarditis) or topically (e.g. for otitis externa).

Adverse effects
- ototoxicity
  - due to auditory or vestibular nerve damage
  - irreversible
- nephrotoxicity
  - accumulates in renal failure
  - the toxicity is secondary to acute tubular necrosis
  - concomitant use of furosemide increases the risk
  - lower doses and more frequent monitoring is required

Contraindications
- myasthenia gravis

Dosing
- due to the significant ototoxic and nephrotoxic potential of gentamicin it is important to monitor plasma concentrations
- both peak (1 hour after administration) and trough levels (just before the next dose) are measured
- if the trough (pre-dose) level is high the interval between the doses should be increased
- if the peak (post-dose) level is high the dose should be decreased

## MACROLIDES

Erythromycin was the first macrolide used clinically. Newer examples include clarithromycin and azithromycin.

Macrolides act by inhibiting bacterial protein synthesis by blocking translocation. If pushed to give an answer they are bacteriostatic in nature, but in reality this depends on the dose and type of organism being treated.

Mechanism of resistance
- post-transcriptional methylation of the 23S bacterial ribosomal RNA

Adverse effects
- prolongation of the QT interval
- gastrointestinal side-effects are common. Nausea is less common with clarithromycin than erythromycin
- cholestatic jaundice: risk may be reduced if erythromycin stearate is used
- P450 inhibitor (see below)
- azithromycin is associated with hearing loss and tinnitus

Common interactions
- statins should be stopped whilst taking a course of macrolides. Macrolides inhibit the cytochrome P450 isoenzyme CYP3A4 that metabolises statins. Taking macrolides concurrently with statins significantly increases the risk of myopathy and rhabdomyolysis.

# QUINOLONES

Quinolones are a group of antibiotics which work by inhibiting DNA synthesis and are bactericidal in nature. Examples include:
- ciprofloxacin
- levofloxacin

Mechanism of action
- inhibit topoisomerase II (DNA gyrase) and topoisomerase IV

Mechanism of resistance
- mutations to DNA gyrase, efflux pumps which reduce intracellular quinolone concentration

Adverse effects
- lower seizure threshold in patients with epilepsy
- tendon damage (including rupture) - the risk is increased in patients also taking steroids
- cartilage damage has been demonstrated in animal models and for this reason quinolones are generally avoided (but not necessarily contraindicated) in children
- lengthens QT interval

Contraindications
- Quinolones should generally be avoided in women who are pregnant or breastfeeding
- avoid in G6PD

# TUBERCULOSIS: DRUG SIDE-EFFECTS AND MECHANISM OF ACTION

Rifampicin

- mechanism of action: inhibits bacterial DNA dependent RNA polymerase preventing transcription of DNA into mRNA
- potent liver enzyme inducer
- hepatitis, orange secretions
- flu-like symptoms

Isoniazid

- mechanism of action: inhibits mycolic acid synthesis
- peripheral neuropathy: prevent with pyridoxine (Vitamin B6)
- hepatitis, agranulocytosis
- liver enzyme inhibitor

Pyrazinamide

- mechanism of action: converted by pyrazinamidase into pyrazinoic acid which in turn inhibits fatty acid synthase (FAS) I
- hyperuricaemia causing gout
- arthralgia, myalgia
- hepatitis

Ethambutol

- mechanism of action: inhibits the enzyme arabinosyl transferase which polymerizes arabinose into arabinan
- optic neuritis: check visual acuity before and during treatment
- dose needs adjusting in patients with renal impairment

# PENICILLIN ALLERGY

Allergy to penicillin based antibiotics is common although many patients who report an allergy may be describing an intolerance/side-effects (e.g. diarrhoea) or a coincidental rash (e.g. amoxicillin in patients with infectious mononucleosis).

Around 0.5-6.5% of patients who are allergic to penicillin are also allergy to cephalosporins. The BNF states the following:

*The principal side-effect of the cephalosporins is hypersensitivity and about 0.5-6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins. Patients with a history of immediate hypersensitivity to penicillin should not receive a cephalosporin. If a cephalosporin is essential in these patients because a suitable alternative antibacterial is not available, then cefixime, cefotaxime, ceftazidime, ceftriaxone, or cefuroxime can be used with caution; cefaclor, cefadroxil, cefalexin, cefradine, and ceftaroline fosamil should be avoided.*

It is important to be aware of other types of penicillin and their trade names to avoid accidental prescription.

Types of penicillin:

- phenoxymethylpenicillin
- benzylpenicillin
- flucloxacillin
- amoxicillin
- ampicillin
- co-amoxiclav (Augmentin)
- co-fluampicil (Magnapen)
- piperacillin with tazobactam (Tazocin)
- ticarcillin with clavulanic acid (Timentin)

# ADRENALINE

Adrenaline is a sympathomimetic amine with both alpha and beta adrenergic stimulating properties

Indications

- anaphylaxis
- cardiac arrest

Recommend Adult Life Support (ALS) adrenaline doses

- anaphylaxis: 0.5ml 1:1,000 IM
- cardiac arrest: 10ml 1:10,000 IV or 1ml of 1:1000 IV

Management of accidental injection

- local infiltration of phentolamine

Background

- responsible for the fight or flight response
- released by the adrenal glands
- acts on α 1 and 2, β 1 and 2 receptors
- acts on β 2 receptors in skeletal muscle vessels-causing vasodilation
- increases cardiac output and total peripheral resistance
- causes vasoconstriction in the skin and kidneys causing a **narrow pulse pressure**

Actions on α adrenergic receptors:

- inhibits insulin secretion by the pancreas
- stimulates glycogenolysis in the liver and muscle
- stimulates glycolysis in muscle

Actions onβ adrenergic receptors:

- stimulates glucagon secretion in the pancreas
- stimulates ACTH
- stimulates lipolysis by adipose tissue

# ASPIRIN

Aspirin works by blocking the action of both cyclooxygenase-1 and 2. Cyclooxygenase is responsible for prostaglandin, prostacyclin and thromboxane synthesis. The blocking of thromboxane A2 formation in platelets reduces the ability of platelets to aggregate which has lead to the widespread use of low-dose aspirin in cardiovascular disease. Until recent guidelines changed all patients with established cardiovascular disease took aspirin if there was no contraindication. Following the 2010 technology appraisal of clopidogrel this is no longer the case*.

Two recent trials (the Aspirin for Asymptomatic Atherosclerosis and the Antithrombotic Trialists Collaboration) have cast doubt on the use of aspirin in primary prevention of cardiovascular disease. Guidelines have not yet changed to reflect this. However the Medicines and Healthcare products Regulatory Agency (MHRA) issued a drug safety update in January 2010 reminding prescribers that aspirin is not licensed for primary prevention.

What do the *current* guidelines recommend?
- first-line for patients with ischaemic heart disease

Potentiates
- oral hypoglycaemics
- warfarin
- steroids

Aspirin should not be used in children under 16 due to the risk of Reye's syndrome. An exception is Kawasaki disease, where the benefits are thought to outweigh the risks.

*NICE now recommend clopidogrel first-line following an ischaemic stroke and for peripheral arterial disease. For TIAs the situation is more complex. Recent Royal College of Physician (RCP) guidelines support the use of clopidogrel in TIAs. However the older NICE guidelines still recommend aspirin + dipyridamole - a position the RCP state is 'illogical'

# HEPARIN

There are two main types of heparin - unfractionated, 'standard' heparin or low molecular weight heparin (LMWH). Heparins generally act by activating antithrombin III. Unfractionated heparin forms a complex which inhibits thrombin, factors Xa, IXa, XIa and XIIa. LMWH however only increases the action of antithrombin III on factor Xa

Adverse effects of heparins include:
- bleeding
- thrombocytopenia - see below
- osteoporosis and an increased risk of fractures

- hyperkalaemia - this is thought to be caused by inhibition of aldosterone secretion

The table below shows the differences between standard heparin and LMWH:

| | Standard heparin | Low molecular weight heparin (LMWH) |
|---|---|---|
| **Administration** | Intravenous | Subcutaneous |
| **Duration of action** | Short | Long |
| **Mechanism of action** | Activates antithrombin III. Forms a complex that inhibits thrombin, factors Xa, IXa, Xia and XIIa | Activates antithrombin III. Forms a complex that inhibits factor Xa |
| **Side-effects** | Bleeding<br>Heparin-induced thrombocytopaenia (HIT)<br>Osteoporosis | Bleeding<br><br>Lower risk of HIT and osteoporosis with LMWH |
| **Monitoring** | Activated partial thromboplastin time (APTT) | Anti-Factor Xa (although routine monitoring is not required) |
| **Notes** | Useful in situations where there is a high risk of bleeding as anticoagulation can be terminated rapidly. Also useful in renal failure | Now standard in the management of venous thromboembolism treatment and prophylaxis and acute coronary syndromes |

Heparin-induced thrombocytopaenia (HIT)
- immune mediated - antibodies form against complexes of platelet factor 4 (PF4) and heparin
- these antibodies bind to the PF4-heparin complexes on the platelet surface and induce platelet activation by cross-linking FcγIIA receptors
- usually does not develop until after 5-10 days of treatment
- despite being associated with low platelets HIT is actually a prothrombotic condition
- features include a greater than 50% reduction in platelets, thrombosis and skin allergy
- treatment options include alternative anticoagulants such as lepirudin and danaparoid

Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.

# OCTREOTIDE

Overview
- long-acting analogue of somatostatin
- somatostatin is released from D cells of pancreas and inhibits the release of growth hormone, glucagon and insulin

Uses

- acute treatment of variceal haemorrhage
- acromegaly
- carcinoid syndrome
- prevent complications following pancreatic surgery
- VIPomas
- refractory diarrhoea

Adverse effects
- gallstones (secondary to biliary stasis)

# ACUTE INTERMITTENT PORPHYRIA: DRUGS

Acute intermittent porphyria (AIP) is an autosomal dominant condition caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem. It characteristically presents with abdominal and neuropsychiatric symptoms in 20-40 year olds. AIP is more common in females (5:1)

Drugs which may precipitate attack
- barbiturates
- halothane
- benzodiazepines
- alcohol
- oral contraceptive pill
- sulphonamides

Drugs considered safe to use
- paracetamol
- aspirin
- codeine
- morphine
- chlorpromazine
- beta-blockers
- penicillin
- metformin

# ST JOHN'S WORT

Overview

- shown to be as effective as tricyclic antidepressants in the treatment of mild-moderate depression
- mechanism: thought to be similar to SSRIs (although noradrenaline uptake inhibition has also been demonstrated)
- NICE advise 'may be of benefit in mild or moderate depression, but its use should not be prescribed or advised because of uncertainty about appropriate doses, variation in the nature of preparations, and potential serious interactions with other drugs'

Adverse effects

- profile in trials similar to placebo
- can cause serotonin syndrome
- inducer of P450 system, therefore decreased levels of drugs such as warfarin, ciclosporin. The effectiveness of the combined oral contraceptive pill may also be reduced

# MOTION SICKNESS

Motion sickness describes the nausea and vomiting which occurs when an apparent discrepancy exists between visually perceived movement and the vestibular systems sense of movement

Management

- the BNF recommends hyoscine (e.g. transdermal patch) as being the most effective treatment. Use is limited due to side-effects
- non-sedating antihistamines such as cyclizine or cinnarizine are recommended in preference to sedating preparation such as promethazine

# COMBINED ORAL CONTRACEPTIVE PILL: ADVANTAGES/DISADVANTAGES

Advantages of combined oral contraceptive pill

- highly effective (failure rate < 1 per 100 woman years)
- doesn't interfere with sex
- contraceptive effects reversible upon stopping
- usually makes periods regular, lighter and less painful
- reduced risk of ovarian, endometrial - this effect may last for several decades after cessation
- reduced risk of colorectal cancer
- may protect against pelvic inflammatory disease
- may reduce ovarian cysts, benign breast disease, acne vulgaris

Disadvantages of combined oral contraceptive pill

- people may forget to take it
- offers no protection against sexually transmitted infections
- increased risk of venous thromboembolic disease
- increased risk of breast and cervical cancer
- increased risk of stroke and ischaemic heart disease (especially in smokers)
- temporary side-effects such as headache, nausea, breast tenderness may be seen

Whilst some users report weight gain whilst taking the combined oral contraceptive pill a Cochrane review did not support a causal relationship.

# COMBINED ORAL CONTRACEPTIVE PILL: CONTRAINDICATIONS

The decision of whether to start a women on the combined oral contraceptive pill is now guided by the UK Medical Eligibility Criteria (UKMEC). This scale categorises the potential cautions and contraindications according to a four point scale, as detailed below:
UKMEC 1: a condition for which there is no restriction for the use of the contraceptive method
UKMEC 2: advantages generally outweigh the disadvantages
UKMEC 3: disadvantages generally outweigh the advantages
UKMEC 4: represents an unacceptable health risk

Examples of UKMEC 3 conditions include

- more than 35 years old and smoking less than 15 cigarettes/day
- BMI > 35 kg/m^2*
- family history of thromboembolic disease in first degree relatives < 45 years
- controlled hypertension
- immobility e.g. wheel chair use
- carrier of known gene mutations associated with breast cancer (e.g. BRCA1/BRCA2)
- current gallbladder disease

Examples of UKMEC 4 conditions include
- more than 35 years old and smoking more than 15 cigarettes/day
- migraine with aura
- history of thromboembolic disease or thrombogenic mutation
- history of stroke or ischaemic heart disease
- breast feeding < 6 weeks post-partum
- uncontrolled hypertension
- current breast cancer
- major surgery with prolonged immobilisation

Diabetes mellitus diagnosed > 20 years ago is classified as UKMEC 3 or 4 depending on severity

Changes in 2016
- breast feeding 6 weeks - 6 months postpartum was changed from UKMEC 3 → 2

# COMBINED ORAL CONTRACEPTIVE PILL: COUNSELLING

Women who are considering taking the combined oral contraceptive pill (COC) should be counselled in a number of areas:

Potential harms and benefits, including
- the COC is > 99% effective if taken correctly
- small risk of blood clots
- very small risk of heart attacks and strokes
- increased risk of breast cancer and cervical cancer

Advice on taking the pill, including
- if the COC is started within the first 5 days of the cycle then there is no need for additional contraception. If it is started at any other point in the cycle then alternative contraception should be used (e.g. condoms) for the first 7 days
- should be taken at the same time every day
- the COCP is conventionally taken for 21 days then stopped for 7 days - similar uterine bleeding to menstruation. However, there was a major change following the 2019 guidelines. 'Tailored' regimes should now be discussed with women. This is because there is no medical benefit from having a withdrawal bleed. Options include never having a pill-free interval or 'tricycling' - taking three 21 day packs back-to-back before having a 4 or 7 day break
- advice that intercourse during the pill-free period is only safe if the next pack is started on time

Discussion on situations where efficacy may be reduced*
- if vomiting within 2 hours of taking COC pill
- medication that induce diarrhoea or vomiting may reduce effectiveness of oral contraception (for example orlistat)

- if taking liver enzyme-inducing drugs

Other information
- discussion on STIs

*Concurrent antibiotic use
- for many years doctors in the UK have advised that the concurrent use of antibiotics may interfere with the enterohepatic circulation of oestrogen and thus make the combined oral contraceptive pill ineffective - 'extra-precautions' were advised for the duration of antibiotic treatment and for 7 days afterwards
- no such precautions are taken in the US or the majority of mainland Europe
- in 2011 the Faculty of Sexual & Reproductive Healthcare produced new guidelines abandoning this approach. The latest edition of the BNF has been updated in line with this guidance
- precautions should still be taken with enzyme inducing antibiotics such as rifampicin

## COMBINED ORAL CONTRACEPTIVE PILL: SPECIAL SITUATIONS

Concurrent antibiotic use
- for many years doctors in the UK have advised that the concurrent use of antibiotics may interfere with the enterohepatic circulation of oestrogen and thus make the combined oral contraceptive pill ineffective - 'extra- precautions' were advised for the duration of antibiotic treatment and for 7 days afterwards
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- in 2011 the Faculty of Sexual & Reproductive Healthcare produced new guidelines abandoning this approach. The latest edition of the BNF has been updated in line with this guidance
- precautions should still be taken with enzyme inducing antibiotics such as rifampicin

Switching combined oral contraceptive pills
- the BNF and Faculty of Sexual & Reproductive Healthcare (FSRH) appear to give contradictory advice. The Clinical Effectiveness Unit of the FSRH have stated in the Combined Oral Contraception guidelines that the pill free interval does not need to be omitted (please see link). The BNF however advises missing the pill free interval if the progesterone changes. Given the uncertainty it is best to follow the BNF

## PROGESTOGEN ONLY PILL: ADVANTAGES/DISADVANTAGES

Advantages
- highly effective (failure rate = 1 per 100 woman years)
- doesn't interfere with sex
- contraceptive effects reversible upon stopping
- can be used whilst breast-feeding

- can be used in situations where the combined oral contraceptive pill is contraindicated e.g. in smokers > 35 years of age and women with a history of venous thromboembolic disease

Disadvantages
- irregular periods: some users may not have periods whilst others may have irregular or light periods. This is the most common adverse effect
- doesn't protect against sexually transmitted infections
- increased incidence of functional ovarian cysts
- common side-effects include breast tenderness, weight gain, acne and headaches. These symptoms generally subside after the first few months

## PHOSPHODIESTERASE TYPE V INHIBITORS

Phosphodiesterase type V (PDE5) inhibitors are used in the treatment of erectile dysfunction. They are also used in the management of pulmonary hypertension. PDE5 inhibitors cause vasodilation through an increase in cGMP leading to smooth muscle relaxation in blood vessels supplying the corpus cavernosum.

Examples
- sildenafil (Viagra) - this was the first phosphodiesterase type V inhibitor
- tadalafil (Cialis)
- vardenafil (Levitra)

Contraindications
- patients taking nitrates and related drugs such as nicorandil
- hypotension
- recent stroke or myocardial infarction (NICE recommend waiting 6 months)

Side-effects
- visual disturbances e.g. blue discolouration, non-arteritic anterior ischaemic neuropathy
- nasal congestion
- flushing
- gastrointestinal side-effects
- headache

The **blue pill**, Viagra (sildenafil), causes **blue discolouration** of vision

## FINASTERIDE

Finasteride is an inhibitor of 5 alpha-reductase, an enzyme which metabolises testosterone into dihydrotestosterone.

Indications

- benign prostatic hyperplasia
- male-pattern baldness

Adverse effects

- impotence
- decrease libido
- ejaculation disorders
- gynaecomastia and breast tenderness

Finasteride causes decreased levels of serum prostate-specific antigen

# ALLOPURINOL

Allopurinol is used in the prevention of gout. It works by inhibiting xanthine oxidase.

Initiating allopurinol prophylaxis - see indications below
- allopurinol should not be started until 2 weeks after an acute attack has settled
- initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of < 300 µmol/l
- NSAID or colchicine cover should be used when starting allopurinol

Indications for allopurinol*
- recurrent attacks - the British Society for Rheumatology recommend 'In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year'
- tophi
- renal disease
- uric acid renal stones
- prophylaxis if on cytotoxics or diuretics

*patients with Lesch-Nyhan syndrome often take allopurinol for life

**Adverse effects**
The most significant adverse effects are dermatological and patients should be warned to stop allopurinol immediately if they develop a rash:
- severe cutaneous adverse reaction (SCAR)
- drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome

Certain ethnic groups such as the Chinese, Korean and Thai people seem to be at an increased risk of these dermatological reactions.

Patients at a high risk of severe cutaneous adverse reaction should be screened for the HLA-B *5801 allele.

**Interactions**
Azathioprine
- metabolised to active compound 6-mercaptopurine
- xanthine oxidase is responsible for the oxidation of 6-mercaptopurine to 6-thiouric acid
- allopurinol can therefore lead to high levels of 6-mercaptopurine
- a much reduced dose (e.g. 25%) must therefore be used if the combination cannot be avoided

Cyclophosphamide
- allopurinol reduces renal clearance, therefore may cause marrow toxicity

Theophylline

- allopurinol causes an increase in plasma concentration of theophylline by inhibiting its breakdown

# TAMOXIFEN

Tamoxifen is a Selective oEstrogen Receptor Modulator (SERM) which acts as an oestrogen receptor antagonist and partial agonist. It is used in the management of oestrogen receptor positive breast cancer

Adverse effects

- menstrual disturbance: vaginal bleeding, amenorrhoea
- hot flushes - 3% of patients stop taking tamoxifen due to climacteric side-effects
- venous thromboembolism
- endometrial cancer
- osteoporosis

Tamoxifen is typically used for 5 years following removal of the tumour.

Raloxifene is a pure oestrogen receptor antagonist, and carries a lower risk of endometrial cancer

# CICLOSPORIN

Ciclosporin is an immunosuppressant which decreases clonal proliferation of T cells by reducing IL-2 release. It acts by binding to cyclophilin forming a complex which inhibits calcineurin, a phosphatase that activates various transcription factors in T cells

Adverse effects of ciclosporin (note how everything is increased - fluid, BP, K+, hair, gums, glucose)

- nephrotoxicity
- hepatotoxicity
- fluid retention
- hypertension
- hyperkalaemia
- hypertrichosis
- gingival hyperplasia
- tremor
- impaired glucose tolerance
- hyperlipidaemia
- increased susceptibility to severe infection

Interestingly for an immunosuppressant, ciclosporin is noted by the BNF to be 'virtually non-myelotoxic'.

Indications
- following organ transplantation
- rheumatoid arthritis
- psoriasis (has a direct effect on keratinocytes as well as modulating T cell function)
- ulcerative colitis
- pure red cell aplasia

# TACROLIMUS

Tacrolimus is a macrolide used as an immunosuppressant to prevent transplant rejection. It has a very similar action to ciclosporin:

Action of ciclosporin
- decreases clonal proliferation of T cells by reducing IL-2 release
- binds to cyclophilin forming a complex which inhibits calcineurin, a phosphotase that activates various transcription factors in T cells

The action of tacrolimus differs in that it binds to a protein called FKBP rather than cyclophilin

Tacrolimus is more potent than ciclosporin and hence the incidence of organ rejection is less. However, nephrotoxicity and impaired glucose tolerance is more common

# IMMUNOGLOBULINS: THERAPEUTICS

The Department of Health issued guidelines on the use of intravenous immunoglobulins in May 2008

Uses
- primary and secondary immunodeficiency
- idiopathic thrombocytopenic purpura
- myasthenia gravis
- Guillain-Barre syndrome
- Kawasaki disease
- toxic epidermal necrolysis
- pneumonitis induced by CMV following transplantation
- low serum IgG levels following haematopoietic stem cell transplant for malignancy
- dermatomyositis
- chronic inflammatory demyelinating polyradiculopathy

Basics
- formed from large pool of donors (e.g. 5,000)
- IgG molecules with a subclass distribution similar to that of normal blood
- half-life of 3 weeks

# MONOCLONAL ANTIBODIES

Monoclonal antibodies have an increasing role in medicine. They are manufactured by a technique called somatic cell hybridization. This involves the fusion of myeloma cells with spleen cells from a mouse that has been immunized with the desired antigen. The resulting fused cells are termed a hybridoma and act as a 'factory' for producing monoclonal antibodies. The main limitation to this is that mouse antibodies are immunogenic leading to the formation of human anti-mouse antibodies (HAMAs). This problem is overcome by combining the variable region from the mouse body with the constant region from an human antibody.

Clinical examples of monoclonal antibodies:

- infliximab (anti-TNF): used in rheumatoid arthritis and Crohn's
- rituximab (anti-CD20): used in non-Hodgkin's lymphoma and rheumatoid arthritis
- cetuximab (epidermal growth factor receptor antagonist): used in metastatic colorectal cancer and head and neck cancer
- trastuzumab (HER2/neu receptor antagonist): used in metastatic breast cancer
- alemtuzumab (anti-CD52): used in chronic lymphocytic leukaemia
- abciximab (glycoprotein IIb/IIIa receptor antagonist): prevention of ischaemic events in patients undergoing percutaneous coronary interventions
- OKT3 (anti-CD3): used to prevent organ rejection

Monoclonal antibodies are also used for:

- medical imaging when combined with a radioisotope
- identification of cell surface markers in biopsied tissue
- diagnosis of viral infections

# TRASTUZUMAB

Trastuzumab (Herceptin) is a monoclonal antibody directed against the HER2/neu receptor. It is used mainly in metastatic breast cancer although some patients with early disease are now also given trastuzumab.

Adverse effects

- flu-like symptoms and diarrhoea are common
- cardiotoxicity: more common when anthracyclines have also been used. An echo is usually performed before starting treatment

# NOVEL PSYCHOACTIVE SUBSTANCES

Novel psychoactive substances is the medical term for the many new substances which are chemically related to established recreational drugs such as MDMA and cannabis. They are often referred to as 'legal highs' although this is a misnomer in the UK, as their distribution and sale have been illegal since 2016.

The information below describes some of the common types:

Stimulants

- similar to MDMA, amphetamines and cocaine, resulting in increased levels of serotonin, dopamine and noradrenaline, resulting in a 'high' and feeling of euphoria
- a common example is a stimulant NPS is mephedrone ('bath salts','M-CAT'.'meow meow'). It is a cathinone and structurally similar to khat, a plant found in East Africa
- another example is benzylpiperazine ('Exodus', 'Legal X', 'Legal E')
- typically swallowed as a pill/powder ('bombing') or snorted
- adverse effect profile similar to MDMA/cocaine, with the risk of serotonin syndrome

Cannabinoids

- termed synthetic cannabinoid receptor agonists
- commonly referred to as 'spice'
- typically sprayed on to herbal mixtures which are then smoked. Also available in liquid form which is then inhaled using e-cigarettes
- similar adverse effects to cannabis

Hallucinogenics

- can be either dissociatives and psychedelics
- dissociatives produce a similar effect to ketamine, with a sense of not being connected to the physical body or time. A common dissociative NPS is methoxetamine ('mexxy')
- psychedelics have a similar effect to LSD although NPS versions may also be a stimulant

Depressant

- can be either opioid or benzodiazepine-based
- usually taken as a pill or a powder
- often structurally very similar to the original drug class, hence the adverse effects are similar
- benzodiazepine NPS often have a significantly longer half-life

Other substances include:

- Gamma-hydroxybutyric acid (GHB) and gamma-butyrolactone (GBL): 'G', 'Geebs' or 'Liquid Ecstasy'
- GHB causes respiratory depression. When taken with other respiratory depressants, most commonly alcohol, this can be potentially life threatening
- Nitrous oxide: 'Hippie crack'

For a more detailed overview please see the excellent review in BMJ 2017;356:i6848

# COCAINE

Cocaine is an alkaloid derived from the coca plant. It is widely used as a recreational stimulant. The price of cocaine has fallen sharply in the past decade resulting in cocaine toxicity becoming a much more frequent clinical problem. This increase has made cocaine a favourite topic of question writers.

Mechanism of action

- cocaine blocks the uptake of dopamine, noradrenaline and serotonin

The use of cocaine is associated with a wide variety of adverse effects:

Cardiovascular effects

- myocardial infarction
- both tachycardia and bradycardia may occur
- hypertension
- QRS widening and QT prolongation
- aortic dissection

Neurological effects

- seizures
- mydriasis
- hypertonia
- hyperreflexia

Psychiatric effects

- agitation
- psychosis
- hallucinations

Others

- ischaemic colitis is recognised in patients following cocaine ingestion. This should be considered if patients complain of abdominal pain or rectal bleeding
- hyperthermia
- metabolic acidosis
- rhabdomyolysis

Management of cocaine toxicity

- in general, benzodiazepines are generally first-line for most cocaine-related problems

- chest pain: benzodiazepines + glyceryl trinitrate. If myocardial infarction develops then primary percutaneous coronary intervention
- hypertension: benzodiazepines + sodium nitroprusside
- the use of beta-blockers in cocaine-induced cardiovascular problems is a controversial issue. The American Heart Association issued a statement in 2008 warning against the use of beta-blockers (due to the risk of unopposed alpha-mediated coronary vasospasm) but many cardiologists since have questioned whether this is valid. If a reasonable alternative is given in an exam it is probably wise to choose it

# ALCOHOL - PROBLEM DRINKING: MANAGEMENT

Nutritional support

- SIGN recommends alcoholic patients should receive oral thiamine if their 'diet may be deficient'

Drugs used

- benzodiazepines for acute withdrawal
- disulfram: promotes abstinence - alcohol intake causes severe reaction due to inhibition of acetaldehyde dehydrogenase. Patients should be aware that even small amounts of alcohol (e.g. In perfumes, foods, mouthwashes) can produce severe symptoms. Contraindications include ischaemic heart disease and psychosis
- acamprosate: reduces craving, known to be a weak antagonist of NMDA receptors, improves abstinence in placebo controlled trials

# METHANOL POISONING

Methanol poisoning causes both the effects associated with alcohol (intoxication, nausea etc) and also specific visual problems, including blindness. These effects are thought to be secondary to the accumulation of formic acid. The actual pathophysiology of methanol-associated visual loss is not fully understood but it is thought to be caused by a form of optic neuropathy

Management

- fomepizole (competitive inhibitor of alcohol dehydrogenase) or ethanol
- haemodialysis

# ETHYLENE GLYCOL TOXICITY

Ethylene glycol is a type of alcohol used as a coolant or antifreeze

Features of toxicity are divided into 3 stages:

- Stage 1: symptoms similar to alcohol intoxication: confusion, slurred speech, dizziness
- Stage 2: metabolic acidosis with high anion gap and high osmolar gap. Also tachycardia, hypertension
- Stage 3: acute kidney injury

Management has changed in recent times

- ethanol has been used for many years
- works by competing with ethylene glycol for the enzyme alcohol dehydrogenase
- this limits the formation of toxic metabolites (e.g. glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning

- fomepizole, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol
- haemodialysis also has a role in refractory cases

# DRUG MONITORING

The tables below show the monitoring requirements of common drugs. It should be noted these are basic guidelines and do not relate to monitoring effectiveness of treatment (e.g. Checking lipids for patients taking a statin)

### Cardiovascular drugs

| Drug | Main monitoring parameters | Details of monitoring |
|---|---|---|
| Statins | LFT | LFTs at baseline, 3 months and 12 months |
| ACE inhibitors | U&E | U&E prior to treatment<br>U&E after increasing dose<br>U&E at least annually |
| Amiodarone | TFT, LFT | TFT, LFT, U&E, CXR prior to treatment<br>TFT, LFT every 6 months |

### Rheumatology drugs

| Drug | Main monitoring parameters | Details of monitoring |
|---|---|---|
| Methotrexate | FBC, LFT, U&E | The Committee on Safety of Medicines recommend 'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months' |
| Azathioprine | FBC, LFT | FBC, LFT before treatment<br>FBC weekly for the first 4 weeks<br>FBC, LFT every 3 months |

### Neuropsychiatric drugs

| Drug | Main monitoring parameters | Details of monitoring |
|---|---|---|
| Lithium | Lithium level, TFT, U&E | TFT, U&E prior to treatment<br>Lithium levels weekly until stabilised then every 3 months<br>TFT, U&E every 6 months |
| Sodium valproate | LFT | LFT, FBC before treatment<br>LFT 'periodically' during first 6 months |

### Endocrine drugs

| Drug | Main monitoring parameters | Details of monitoring |
|---|---|---|
| Glitazones | LFT | LFT before treatment<br>LFT 'regularly' during treatment |

# THERAPEUTIC DRUG MONITORING

Lithium

- range = 0.4 - 1.0 mmol/l
- take 12 hrs post-dose

Ciclosporin

- trough levels immediately before dose

Digoxin

- at least 6 hrs post-dose

Phenytoin levels do not need to be monitored routinely but **trough levels, immediately before dose** should be checked if:

- adjustment of phenytoin dose
- suspected toxicity
- detection of non-adherence to the prescribed medication

# SIDE-EFFECTS OF COMMON DRUGS: ANTI-ANGINALS

The table below summarises characteristic (if not necessarily the most common) side-effects of drugs used to treat angina

| Drug | Side-effect |
|---|---|
| Calcium channel blockers | • Headache<br>• Flushing<br>• Ankle oedema<br><br>Verapamil also commonly causes constipation |
| Beta-blockers | • Bronchospasm (especially in asthmatics)<br>• Fatigue<br>• Cold peripheries<br>• Sleep disturbances |
| Nitrates | • Headache<br>• Postural hypotension<br>• Tachycardia |
| Nicorandil | • Headache<br>• Flushing<br>• Anal ulceration |

# SIDE-EFFECTS OF COMMON DRUGS: DIABETES DRUGS

The table below summarises characteristic (if not necessarily the most common) side-effects of drugs used to treat diabetes mellitus

| Drug | Side-effect |
|---|---|
| Metformin | Gastrointestinal side-effects<br>Lactic acidosis |
| Sulfonylureas | Hypoglycaemic episodes<br>Increased appetite and weight gain<br>Syndrome of inappropriate ADH secretion<br>Liver dysfunction (cholestatic) |
| Glitazones | Weight gain<br>Fluid retention<br>Liver dysfunction<br>Fractures |
| Gliptins | Pancreatitis |

# DRUG CAUSES OF AGRANULOCYTOSIS

Common drugs that cause agranulocytosis:

- Antithyroid drugs - carbimazole, propylthiouracil
- Antipsychotics - atypical antipsychotics (CLOZAPINE)
- Antiepileptics - carbamazepine
- Antibiotics - penicillin, chloramphenicol, co-trimoxazole
- Antidepressant - mirtazapine
- Cytotoxic drugs - methotrexate

# DRUG CAUSES OF URTICARIA

The following drugs commonly cause urticaria:
aspirin
penicillins
NSAIDs
opiates

# DRUG-INDUCED IMPAIRED GLUCOSE TOLERANCE

Drugs which are known to cause impaired glucose tolerance include:

- thiazides, furosemide (less common)
- steroids
- tacrolimus, ciclosporin
- interferon-alpha
- nicotinic acid
- antipsychotics

Beta-blockers cause a slight impairment of glucose tolerance. They should also be used with caution in diabetics as they can interfere with the metabolic and autonomic responses to hypoglycaemia

# DRUG-INDUCED THROMBOCYTOPENIA

Drug-induced thrombocytopenia (probable immune-mediated)

- quinine
- abciximab
- NSAIDs
- diuretics: furosemide
- antibiotics: penicillins, sulphonamides, rifampicin
- anticonvulsants: carbamazepine, valproate

- heparin

# DRUG-INDUCED URINARY RETENTION

The following drugs may cause urinary retention:
- tricyclic antidepressants
- anticholinergics
- opioids
- NSAIDs
- disopyramide

# DRUGS CAUSING LUNG FIBROSIS

Causes
- amiodarone
- cytotoxic agents: busulphan, bleomycin
- anti-rheumatoid drugs: methotrexate, sulfasalazine
- nitrofurantoin
- ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide)

# DRUGS CAUSING OCULAR PROBLEMS

Cataracts
- steroids

Corneal opacities
- amiodarone
- indomethacin

Optic neuritis
- ethambutol
- amiodarone
- metronidazole

Retinopathy
- chloroquine, quinine

Sildenafil can cause both blue discolouration and non-arteritic anterior ischaemic neuropathy

# DRUGS CAUSING PHOTOSENSITIVITY

Causes of drug-induced photosensitivity
- thiazides
- tetracyclines, sulphonamides, ciprofloxacin
- amiodarone
- NSAIDs e.g. piroxicam
- psoralens
- sulphonylureas

# AMIODARONE AND THE THYROID GLAND

Around 1 in 6 patients taking amiodarone develop thyroid dysfunction

**Amiodarone-induced hypothyroidism**
The pathophysiology of amiodarone-induced hypothyroidism (AIH) is thought to be due to the high iodine content of amiodarone causing a Wolff-Chaikoff effect*

Amiodarone may be continued if this is desirable

**Amiodarone-induced thyrotoxicosis**
Amiodarone-induced thyrotoxicosis (AIT) may be divided into two types:

| | AIT type 1 | AIT type 2 |
|---|---|---|
| Pathophysiology | Excess iodine-induced thyroid hormone synthesis | Amiodarone-related destructive thyroiditis |
| Goitre | Present | Absent |
| Management | Carbimazole or potassium perchlorate | Corticosteroids |

Unlike in AIH, amiodarone should be stopped if possible in patients who develop AIT

*an autoregulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide

# OCULOGYRIC CRISIS

An oculogyric crisis is a dystonic reaction to certain drugs or medical conditions

Features
- restlessness, agitation

- involuntary upward deviation of the eyes

Causes

- antipsychotics
- metoclopramide
- postencephalitic Parkinson's disease

Management

- intravenous antimuscarinic: benztropine or procyclidine

# SEROTONIN SYNDROME

Causes

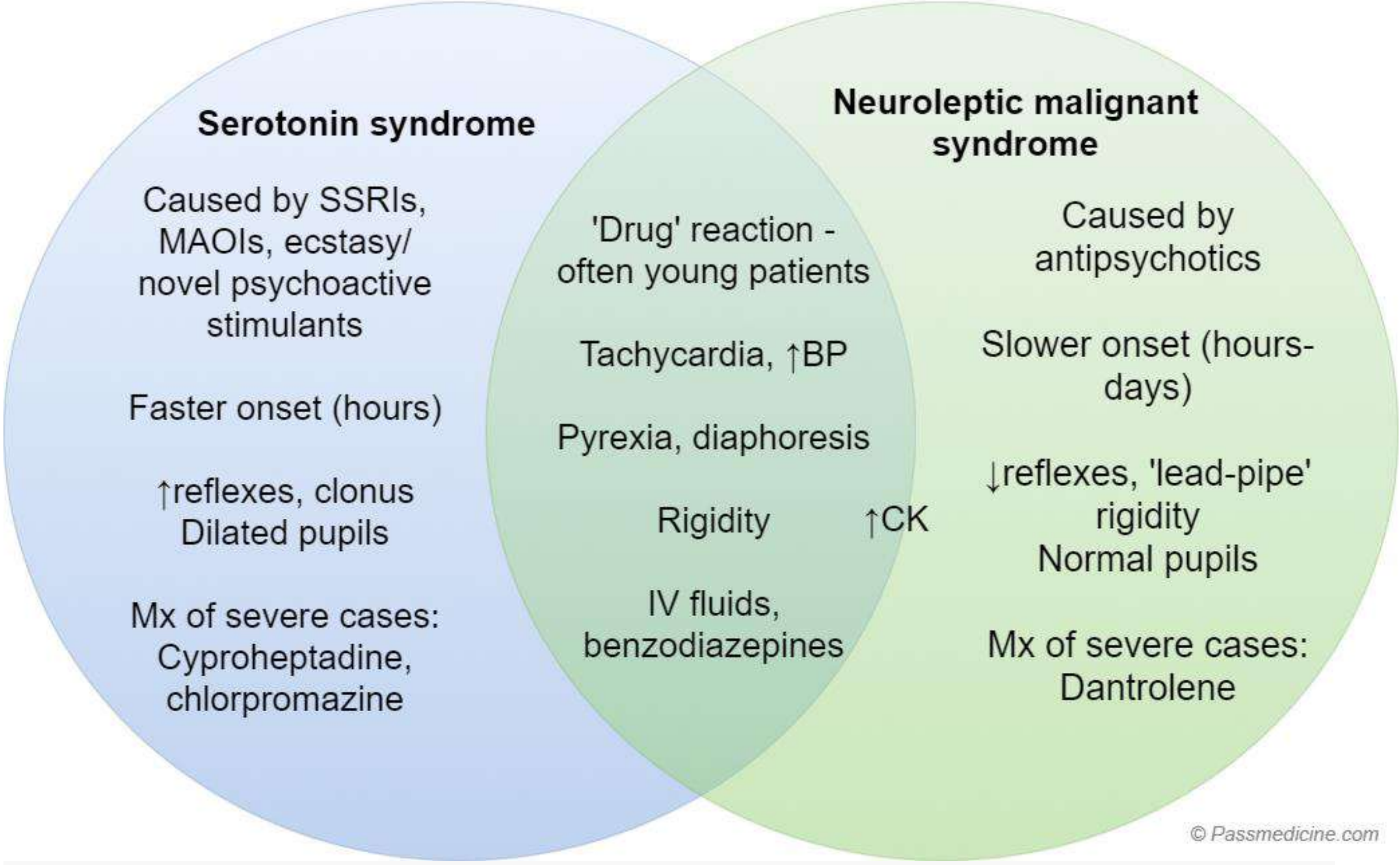
- monoamine oxidase inhibitors
- SSRIs
  - St John's Wort, often taken over the counter for depression, can interact with SSRIs to cause serotonin syndrome
- ecstasy
- amphetamines

Features

- neuromuscular excitation (e.g. hyperreflexia, myoclonus, rigidity)
- autonomic nervous system excitation (e.g. hyperthermia)
- altered mental state

Management

- supportive including IV fluids
- benzodiazepines
- more severe cases are managed using serotonin antagonists such as cyproheptadine and chlorpromazine


Serotonin syndrome
Caused by SSRIs, MAOIs, ecstasy/ novel psychoactive stimulants
Faster onset (hours)
↑reflexes, clonus
Dilated pupils
Mx of severe cases: Cyproheptadine, chlorpromazine
'Drug' reaction - often young patients
Tachycardia, ↑BP
Pyrexia, diaphoresis
Rigidity
↑CK
IV fluids, benzodiazepines
Neuroleptic malignant syndrome
Caused by antipsychotics
Slower onset (hours-days)
↓reflexes, 'lead-pipe' rigidity
Normal pupils
Mx of severe cases: Dantrolene
© Passmedicine.com

Venn diagram showing contrasting serotonin syndrome with neuroleptic malignant syndrome. Note that both conditions can cause a raised creatine kinase (CK) but it tends to be more associated with NMS.

## DRESS SYNDROME

DRESS is an unexpected, severe reaction to medication. Several organs are commonly affected including the skin, liver, kidneys, lungs and heart. Not all of these organs may be affected at any one time.

Classically patients develop a morbilliform skin rash in 80% cases which often leads to an exfoliative dermatitis, high fever, and inflammation of one or more organs. Vesicles and bullae may be seen. Erythroderma can occur in 10% of cases, mucosal involvement in 25% and facial swelling in 30%. The reaction usually occurs 2-8 weeks after commencing the offending drug.

Patients may develop systematic symptoms which can include haematological abnormalities (raised and low white count, eosinophilia (in 30% this is > 2.0 * 109 /L, thrombocytopaenia, anaemia, atypical lymphocytes), enlarged lymph nodes (75%), 10% develop kidney disease which is usually mild (interstitial nephritis is common, renal failure is rare), myocarditis, pericarditis, liver enlargement, hepatitis and rarely hepatic necrosis with liver failure (abnormal liver function tests are found in 70-90% in particularly raised transaminases), lung disease (pneumonitis, pleuritis, pneumonia), neurological involvement which may lead to meningitis and encephalitis, gastrointestinal symptoms, in severe cases, acute colitis and pancreatitis can occur, and endocrine abnormalities may include thyroiditis and diabetes.

Diagnosis can be very difficult and it may also be difficult to determine the exact drug causing the hypersensitivity as first exposure may have started 8 weeks prior. Common drugs causing DRESS include allopurinol, anti-epileptics, antibiotics, immunosuppresants, HIV treatment and NSAIDS. A careful drug history should be taken.

The diagnosis should be suspected when there is presence of the triad of extensive skin rash, high fever, and organ involvement, supported by a finding of eosinophilia and abnormal liver function tests. RegiSCAR has proposed a diagnostic criteria and patients require at least 3 of the following:

- Hospitalisation
- Reaction suspected to be drug related
- Acute skin rash
- Fever about 38ºC
- Enlarged lymph nodes at two sites
- Involvement of at least one internal organ
- Blood count abnormalities such as low platelets, raised eosinophils or abnormal lymphocyte count.

Skin biopsy can help to confirm the diagnosis. This may show inflammatory infiltrate in particularly eosinophils, extravasated erythrocytes and oedema. Regular blood tests including FBC, clotting, liver and renal function, CK, viral screen, glucose and thyroid function tests should be taken. Investigations looking for complications should be undertaken including ECG, CXR, echocardiogram, and urinalysis.

DRESS syndrome treatment requires all medications that are a possible culprits to be stopped and supportive care started. Antihistamines, topical steroids and emollients can be used to help control the rash. Careful fluid balance is necessary and clinicians should be aware of the patients nutritional status. Skin should be regularly checked and secondary infections should be treated with antibiotics. Systemic steroids may be started in severe cases where exfoliative dermatitis / pneumonitis / hepatitis is present. Occasionally immunosuppressants, intravenous immunoglobulin and plasmapheresis may be started. Potential culprit drugs should not be restarted again. The mortality is around 8%.

# OVERDOSE AND POISONING: MANAGEMENT

The table below outlines the main management for common overdoses:

| Toxin | Treatment |
|---|---|
| **Paracetamol** | Management<br>• activated charcoal if ingested < 1 hour ago<br>• N-acetylcysteine (NAC)<br>• liver transplantation |
| **Salicylate** | Management<br>• urinary alkalinization is now rarely used - it is contraindicated in cerebral and pulmonary oedema with most units now proceeding straight to haemodialysis in cases of severe poisoning<br>• haemodialysis |
| **Opioid/opiates** | Naloxone |
| **Benzodiazepines** | Flumazenil<br>The majority of overdoses are managed with supportive care only due to the risk of seizures with flumazenil. It is generally only used with severe or iatrogenic overdoses. |
| **Tricyclic antidepressants** | Management<br>• IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity<br>• arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias<br>• dialysis is ineffective in removing tricyclics |
| **Lithium** | Management<br>• mild-moderate toxicity may respond to volume resuscitation with normal saline<br>• haemodialysis may be needed in severe toxicity |

| Toxin | Treatment |
|---|---|
| | • sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion |
| **Warfarin** | Vitamin K, prothrombin complex |
| **Heparin** | Protamine sulphate |
| **Beta-blockers** | Management<br>• if bradycardic then atropine<br>• in resistant cases glucagon may be used |
| **Ethylene glycol** | Management has changed in recent times<br>• ethanol has been used for many years<br>• works by competing with ethylene glycol for the enzyme alcohol dehydrogenase<br>• this limits the formation of toxic metabolites (e.g. Glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning<br>• **fomepizole**, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol<br>• haemodialysis also has a role in refractory cases |
| **Methanol poisoning** | Management<br>• fomepizole or ethanol<br>• haemodialysis |
| **Organophosphate insecticides** | Management<br>• atropine<br>• the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit |
| **Digoxin** | Digoxin-specific antibody fragments |
| **Iron** | Desferrioxamine, a chelating agent |
| **Lead** | Dimercaprol, calcium edetate |
| **Carbon monoxide** | Management<br>• 100% oxygen |

| Toxin | Treatment |
|---|---|
|  | - hyperbaric oxygen |
| **Cyanide** | Hydroxocobalamin; also combination of amyl nitrite, sodium nitrite, and sodium thiosulfate |

# HAEMODIALYSIS IN OVERDOSE

Drugs that can be cleared with haemodialysis - mnemonic: BLAST

- Barbiturate
- Lithium
- Alcohol (inc methanol, ethylene glycol)
- Salicylates
- Theophyllines (charcoal haemoperfusion is preferable)

Drugs which cannot be cleared with haemodialysis include

- tricyclics
- benzodiazepines
- dextropropoxyphene (Co-proxamol)
- digoxin
- beta-blockers

# PARACETAMOL OVERDOSE: RISK FACTORS

The following groups of patients are at an increased risk of developing hepatotoxicity following a paracetamol overdose:

- patients taking liver enzyme-inducing drugs (rifampicin, phenytoin, carbamazepine, chronic alcohol excess, St John's Wort)
- malnourished patients (e.g. anorexia nervosa) or patients who have not eaten for a few days

Interestingly, acute alcohol intake, as opposed to chronic alcohol excess, is not associated with an increased risk of developing hepatotoxicity and may actually be protective.

# PARACETAMOL OVERDOSE: METABOLIC PATHWAYS

The liver normally conjugates paracetamol with glucuronic acid/sulphate. During an overdose the conjugation system becomes saturated leading to oxidation by P450 mixed function oxidases*. This produces a toxic metabolite (N-acetyl-B-benzoquinone imine)

Normally glutathione acts as a defence mechanism by conjugating with the toxin forming the non-toxic mercapturic acid. If glutathione stores run-out, the toxin forms covalent bonds with cell proteins, denaturing them and leading to cell death. This occurs not only in hepatocytes but also in the renal tubules

N-acetyl cysteine is used in the management of paracetamol overdose as it is a precursor of glutathione and hence can increase hepatic glutathione production

*this explains why there is a lower threshold for treating patients who take P450 inducing medications e.g. phenytoin or rifampicin

## PARACETAMOL OVERDOSE: MANAGEMENT

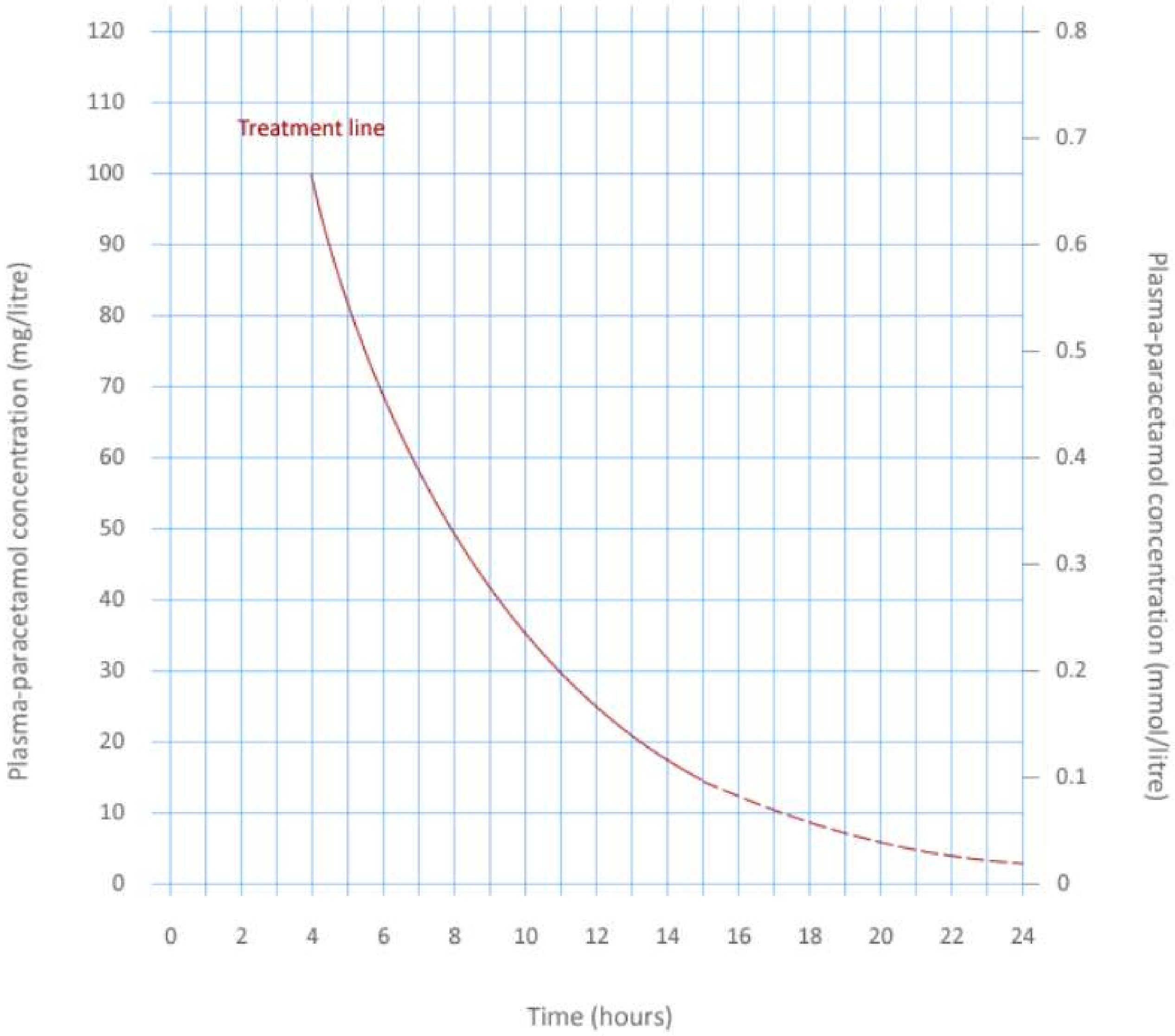
The following is based on 2012 Commission on Human Medicines (CHM) review of paracetamol overdose management. The big change in these guidelines was the removal of the 'high-risk' treatment line on the normogram. All patients are therefore treated the same regardless of risk factors for hepatotoxicity. The National Poisons Information Service/TOXBASE should always be consulted for situations outside of the normal parameters.

The minority of patients who present within 1 hour may benefit from activated charcoal to reduce absorption of the drug.

Acetylcysteine should be given if:

- there is a staggered overdose* or there is doubt over the time of paracetamol ingestion, regardless of the plasma paracetamol concentration; or
- the plasma paracetamol concentration is on or above a single treatment line joining points of 100 mg/L at 4 hours and 15 mg/L at 15 hours, regardless of risk factors of hepatotoxicity

Acetylcysteine is now infused over 1 hour (rather than the previous 15 minutes) to reduce the number of adverse effects. Acetylcysteine commonly causes an anaphylactoid reaction (non-IgE mediated mast cell release). Anaphylactoid reactions to IV acetylcysteine are generally treated by stopping the infusion, then restarting at a slower rate.



**King's College Hospital criteria for liver transplantation (paracetamol liver failure)**

**Arterial pH < 7.3, 24 hours after ingestion**

**or all of the following:**

- **prothrombin time > 100 seconds**
- **creatinine > 300 µmol/l**
- **grade III or IV encephalopathy**

*an overdose is considered staggered if all the tablets were not taken within 1 hour

# SALICYLATE OVERDOSE

A key concept for the exam is to understand that salicylate overdose leads to a mixed respiratory alkalosis and metabolic acidosis. Early stimulation of the respiratory centre leads to a respiratory alkalosis whilst later the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis. In children metabolic acidosis tends to predominate.

Features
- hyperventilation (centrally stimulates respiration)
- tinnitus
- lethargy
- sweating, pyrexia*
- nausea/vomiting
- hyperglycaemia and hypoglycaemia
- seizures
- coma

Treatment
- general (ABC, charcoal)
- urinary alkalinization with intravenous sodium bicarbonate - enhances elimination of aspirin in the urine
- haemodialysis

Indications for haemodialysis in salicylate overdose
- serum concentration > 700mg/L
- metabolic acidosis resistant to treatment
- acute renal failure
- pulmonary oedema
- seizures
- coma

*salicylates cause the uncoupling of oxidative phosphorylation leading to decreased adenosine triphosphate production, increased oxygen consumption and increased carbon dioxide and heat production

## BETA-BLOCKER OVERDOSE

Features
- bradycardia
- hypotension
- heart failure
- syncope

Management
- if bradycardic then atropine
- in resistant cases glucagon may be used

Haemodialysis is not effective in beta-blocker overdose

# TRICYCLIC OVERDOSE

Overdose of tricyclic antidepressants is a common presentation to emergency departments. Amitriptyline and dosulepin (dothiepin) are particularly dangerous in overdose.

Early features relate to anticholinergic properties: dry mouth, dilated pupils, agitation, sinus tachycardia, blurred vision.

Features of severe poisoning include:
- arrhythmias
- seizures
- metabolic acidosis
- coma

ECG changes include:
- sinus tachycardia
- widening of QRS
- prolongation of QT interval

Widening of QRS > 100ms is associated with an increased risk of seizures whilst QRS > 160ms is associated with ventricular arrhythmias

Management
- IV bicarbonate
    - first-line therapy for hypotension or arrhythmias
    - indications include widening of the QRS interval >100 msec or a ventricular arrhythmia
- other drugs for arrhythmias

+ class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation
- class III drugs such as amiodarone should also be avoided as they prolong the QT interval
- response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias
- intravenous lipid emulsion is increasingly used to bind free drug and reduce toxicity
- dialysis is ineffective in removing tricyclics

# LITHIUM TOXICITY

Lithium is a mood stabilising drug used most commonly prophylactically in bipolar disorder but also as an adjunct in refractory depression. It has a very narrow therapeutic range (0.4-1.0 mmol/L) and a long plasma half-life being excreted primarily by the kidneys. Lithium toxicity generally occurs following concentrations > 1.5 mmol/L.

Toxicity may be precipitated by:

- dehydration
- renal failure
- drugs: diuretics (especially thiazides), ACE inhibitors/angiotensin II receptor blockers, NSAIDs and metronidazole.

Features of toxicity

- coarse tremor (a fine tremor is seen in therapeutic levels)
- hyperreflexia
- acute confusion
- seizure
- coma

Management

- mild-moderate toxicity may respond to volume resuscitation with normal saline
- haemodialysis may be needed in severe toxicity
- sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion

# HYPOMAGNESAEMIA

Cause of low magnesium

- drugs: diuretics, proton pump inhibitors
- total parenteral nutrition
- diarrhoea
- alcohol
- hypokalaemia, hypocalcaemia
- conditions causing diarrhoea: Crohn's, ulcerative colitis
- metabolic disorders: Gitleman's and Bartter's

Features may be similar to hypocalcaemia:

- paraesthesia
- tetany
- seizures

- arrhythmias
- decreased PTH secretion → hypocalcaemia
- ECG features similar to those of hypokalaemia
- exacerbates digoxin toxicity

**Treatment**
<0.4 mmol/l

- intravenous replacement is commonly given. An example regime would be 40 mmol of magnesium sulphate over 24 hours

>0.4 mmol/l

- oral magnesium salts (10-20 mmol orally per day)
- diarrhoea can occur with oral magnesium salts

# ECSTASY POISONING

Ecstasy (MDMA, 3,4-Methylenedioxymethamphetamine) use became popular in the 1990's during the emergence of dance music culture

Clinical features

- neurological: agitation, anxiety, confusion, ataxia
- cardiovascular: tachycardia, hypertension
- hyponatraemia
- hyperthermia
- rhabdomyolysis

Management

- supportive
- dantrolene may be used for hyperthermia if simple measures fail

# ORGANOPHOSPHATE INSECTICIDE POISONING

One of the effects of organophosphate poisoning is inhibition of acetylcholinesterase leading to upregulation of nicotinic and muscarinic cholinergic neurotransmission. In warfare, sarin gas is a highly toxic synthetic organophosphorus compound that has similar effects.

Features can be predicted by the accumulation of acetylcholine (mnemonic = SLUD)

- Salivation
- Lacrimation
- Urination

- Defecation/diarrhoea
- cardiovascular: hypotension, bradycardia
- also: small pupils, muscle fasciculation

Management
- atropine
- the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit

# QUININE TOXICITY (CINCHONISM)

Quinine is a remarkably toxic drug; something which is not so readily acknowledged. It is used as an antimalarial drug and also as a prophylactic agent against leg cramps, although both uses are increasingly falling from vogue due to the availability of better, safer agents. Quinine toxicity, known as cinchonism, may be fatal, usually by cardiac arrhythmia or flash pulmonary oedema in the short term, although incipient renal failure may be fatal more long-term.

**Cardiac arrhythmia** is a common finding in cinchonism due to blockade of sodium and potassium channels prolonging QRS and QT intervals respectively and these rhythms may degenerate into ventricular tachyarrhythmias or fibrillation causing death. **Hypoglycaemia** is also a common finding in cinchonism since quinine stimulates pancreatic insulin secretion and this should be corrected rapidly if present. Unlike in the above case, flash pulmonary oedema may develop causing hypoxia and necessitating positive pressure ventilation. Classical hallmarks of cinchonism are tinnitus, visual blurring, flushed and dry skin and abdominal pain.

Clinically, quinine toxicity is difficult to distinguish from aspirin poisoning and so measurement of serum salicylate levels is important when this clinical picture is seen. In terms of management however, whereas aspirin can be cleared from overdose victims by haemofiltration, quinine cannot be extracted easily by extracorporeal methods. Central nervous symptoms such as tinnitus, deafness and visual defects which may occur with aspirin are usually transient whereas quinine leaves permanent neural damage, if the patient survives.

Management of quinine poisoning is largely supportive with fluids, inotropes and bicarbonate as needed as well as positive pressure ventilation for pulmonary oedema.

# CAUSTIC SUBSTANCE INGESTION

Caustic (corrosive) substance ingestion is a common emergency department presentation in adults and children. The majority of cases are accidental exposures to household products: these are usually of little clinical consequence. Conversely, significant morbidity can occur when the substance is consumed in larger quantities with the intention of deliberate self-harm.

Types of substance* - vital to obtain bottle/label if possible

- Oxidising agents, e.g. hydrogen peroxide, sodium hypochlorite (found in household bleach)
- Strong alkali, e.g. sodium hydroxide, potassium hydroxide (found in dishwasher cleaner, industrial cleaners) -> liquefactive necrosis, more commonly resulting in oesophageal injury
- Strong acid, e.g. hydrochloric, nitric acid (found in car batteries, WC cleaner) -> coagulative necrosis, more commonly resulting in gastric injury

Acute management 1 - (general principles, local guidance on timing of endoscopy and PPI may vary)

- ABCDE approach, particular caution to airway swelling and compromise, look for peri-oral oedema
- Urgent upper GI surgical referral if signs of perforation present (surgical emphysema, mediastinal widening on chest x-ray)
- Neutralisation of ingested substance (e.g. with milk) should be avoided as the resulting exothermic reaction will release heat and may cause further injury
- High dose IV PPI
- Symptomatic ingestion (drooling, vomiting, dysphagia, odynophagia, chest pain) requires urgent assessment with upper GI endoscopy to assess the degree of ulceration (Zargar classification). Extensive injury on endoscopy should prompt consideration of urgent surgical exploration
- Asymptomatic ingestion can usually be discharged after a trial of oral fluid and a period of observation

**Complications**

Acute

- Upper GI ulceration, perforation
- Upper airway injury and compromise
- Aspiration pneumonitis
- Infection
- Electrolyte disturbance (e.g. hypocalcaemia in hydrofluoric acid ingestion)

Chronic

- Strictures, fistulae, gastric outlet obstruction
- Upper GI carcinoma (estimated 1000-3000 fold increased risk)

*Please refer to National Poisons Information/toxbase for specific management

**References**

1. Bonnici, K., Wood, D. and Dargan, P. (2014). Should computerised tomography replace endoscopy in the evaluation of symptomatic ingestion of corrosive substances?. Clinical Toxicology, 52(9), pp.911-925.

# CARBON MONOXIDE POISONING

Carbon monoxide has a high affinity for haemoglobin and myoglobin resulting in a left-shift of the oxygen dissociation curve and tissue hypoxia. There are approximately 50 per year deaths from accidental carbon monoxide poisoning in the UK.

Pathophysiology
- in carbon monoxide poisoning the oxygen saturation of haemoglobin decreases leading to an early plateau in the oxygen dissociation curve

Questions may hint at badly maintained housing e.g. student houses.

Features of carbon monoxide toxicity
- headache: 90% of cases
- nausea and vomiting: 50%
- vertigo: 50%
- confusion: 30%
- subjective weakness: 20%
- severe toxicity: 'pink' skin and mucosae, hyperpyrexia, arrhythmias, extrapyramidal features, coma, death

Investigations
- pulse oximetry may be falsely high due to similarities between oxyhaemoglobin and carboxyhaemoglobin
- therefore a venous or arterial blood gas should be taken
- typical carboxyhaemoglobin levels
  - < 3% non-smokers
  - < 10% smokers
  - 10 - 30% symptomatic: headache, vomiting
  - > 30% severe toxicity
- an ECG is a useful supplementary investgation to look for cardiac ischaemia

Management
- patients with suspected carbon monoxide poisoning should be assessed in the emergency department
- 100% high-flow oxygen via a non-rebreather mask
  - from a physiological perspective, this decreases the half-life of carboxyhemoglobin (COHb)

  - should be administered as soon as possible, with treatment continuing for a minimum of six hours
  - target oxygen saturations are 100%
  - treatment is generally continued until all symptoms have resolved, rather than monitoring CO levels
- hyperbaric oxygen
  - due to the small number of cases the evidence base is limited, but there is some evidence that long-term outcomes may be better than standard oxygen therapy for more severe cases
  - therefore, discussion with a specialist should be considered for more severe cases (e.g. levels > 25%)
  - in 2008, the Department of Health publication 'Recognising Carbon Monoxide Poisoning' also listed loss of consciousness at any point, neurological signs other than headache, myocardial ischaemia or arrhythmia and pregnancy as indications for hyperbaric oxygen

## CYANIDE POISONING

Cyanide may be used in insecticides, photograph development and the production of certain metals. Cyanide inhibits the enzyme cytochrome c oxidase, resulting in cessation of the mitochondrial electron transfer chain.

Presentation
- 'classical' features: brick-red skin, smell of bitter almonds
- acute: hypoxia, hypotension, headache, confusion
- chronic: ataxia, peripheral neuropathy, dermatitis

Management
- supportive measures: 100% oxygen
- definitive: hydroxocobalamin (intravenously), also combination of amyl nitrite (inhaled), sodium nitrite (intravenously), and sodium thiosulfate (intravenously)

## MERCURY POISONING

Features
- paraesthesia
- visual field defects
- hearing loss
- irritability
- renal tubular acidosis

# BOTULINUM TOXIN

As well as the well-publicised cosmetic uses of Botulinum toxin ('Botox') there are also a number of licensed indications:

- blepharospasm
- hemifacial spasm
- focal spasticity including cerebral palsy patients, hand and wrist disability associated with stroke
- spasmodic torticollis
- severe hyperhidrosis of the axillae
- achalasia

# PASSMEDICINE NOTES
# CARDIOLOGY

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# CHEST PAIN: ASSESSMENT OF PATIENTS WITH SUSPECTED CARDIAC CHEST PAIN

NICE updated it's guidelines in 2016 on the 'Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin'.

Below is a brief summary of the key points. Please see the link for more details.

**Patients presenting with acute chest pain**

Immediate management of suspected acute coronary syndrome (ACS)

- glyceryl trinitrate
- aspirin 300mg. NICE do not recommend giving other antiplatelet agents (i.e. Clopidogrel) outside of hospital
- do not routinely give oxygen, only give if sats < 94%*
- perform an ECG as soon as possible but do not delay transfer to hospital. A normal ECG does not exclude ACS

Referral

- current chest pain or chest pain in the last 12 hours with an abnormal ECG: emergency admission
- chest pain 12-72 hours ago: refer to hospital the same-day for assessment
- chest pain > 72 hours ago: perform full assessment with ECG and troponin measurement before deciding upon further action

*NICE suggest the following in terms of oxygen therapy:

- do not routinely administer oxygen, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:
- people with oxygen saturation ($SpO_2$) of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for $SpO_2$ of 94-98%
- people with chronic obstructive pulmonary disease who are at risk of hypercapnic respiratory failure, to achieve a target $SpO_2$ of 88-92% until blood gas analysis is available.

**Patients presenting with stable chest pain**

NICE define anginal pain as the following:

1. constricting discomfort in the front of the chest, or in the neck, shoulders, jaw or arms

2. precipitated by physical exertion
3. relieved by rest or GTN in about 5 minutes

  - patients with all 3 features have typical angina
  - patients with 2 of the above features have atypical angina
  - patients with 1 or none of the above features have non-anginal chest pain

For patients in whom stable angina cannot be excluded by clinical assessment alone NICE recommend the following (e.g. symptoms consistent with typical/atypical angina OR ECG changes):
1st line: CT coronary angiography
2nd line: non-invasive functional imaging (looking for reversible myocardial ischaemia)
3rd line: invasive coronary angiography

Examples of non-invasive functional imaging:

- myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT) or
- stress echocardiography or
- first-pass contrast-enhanced magnetic resonance (MR) perfusion or
- MR imaging for stress-induced wall motion abnormalities

# ACUTE CORONARY SYNDROME: A VERY BASIC INTRODUCTION

Acute coronary syndrome (ACS) is an umbrella term covering a number of acute presentations of ischaemic heart disease.

It covers a number of presentations, including

- ST elevation myocardial infarction (STEMI)
- non-ST elevation myocardial infarction (NSTEMI)
- unstable angina

Before we go into more detail into these presentations it's useful to take a step back and consider how such conditions develop.

ACS generally develops in patients who have ischaemic heart disease, either known or previously undetected. Ischaemic heart disease is a term synonymous with coronary heart disease and coronary artery disease. It describes the gradually build up of fatty plaques within the walls of the coronary arteries. This leads to two main problems:

- Gradual narrowing, resulting in less blood and therefore oxygen reaching the myocardium at times of increased demand. This results in angina, i.e. chest pain due to insufficient oxygen reaching the myocardium during exertion
- The risk of sudden plaque rupture. The fatty plaques which have built up in the endothelium may rupture leading to sudden occlusion of the artery. This can result in no blood/oxygen reaching the area of myocardium.

Remember that there are a large number of factors which can increase the chance of a patient developing ischaemic heart disease:

| Unmodifiable risk factors | Modifiable risk factors |
|---|---|
| Increasing age<br>Male gender<br>Family history | Smoking<br>Diabetes mellitus<br>Hypertension<br>Hypercholesterolaemia<br>Obesity |

**Pathophysiology**

Ischaemic heart disease is a complex process which develops over a number of years. A number of changes can be seen:

- initial endothelial dysfunction is triggered by a number of factors such as smoking, hypertension and hyperglycaemia
- this results in a number of changes to the endothelium including pro-inflammatory, pro-oxidant, proliferative and reduced nitric oxide bioavailability
- fatty infiltration of the subendothelial space by low-density lipoprotein (LDL) particles
- monocytes migrate from the blood and differentiate into macrophages. These macrophages then phagocytose oxidized LDL, slowly turning into large 'foam cells'. As these macrophages die the result can further propagate the inflammatory process.
- smooth muscle proliferation and migration from the tunica media into the intima results in formation of a fibrous capsule covering the fatty plaque.

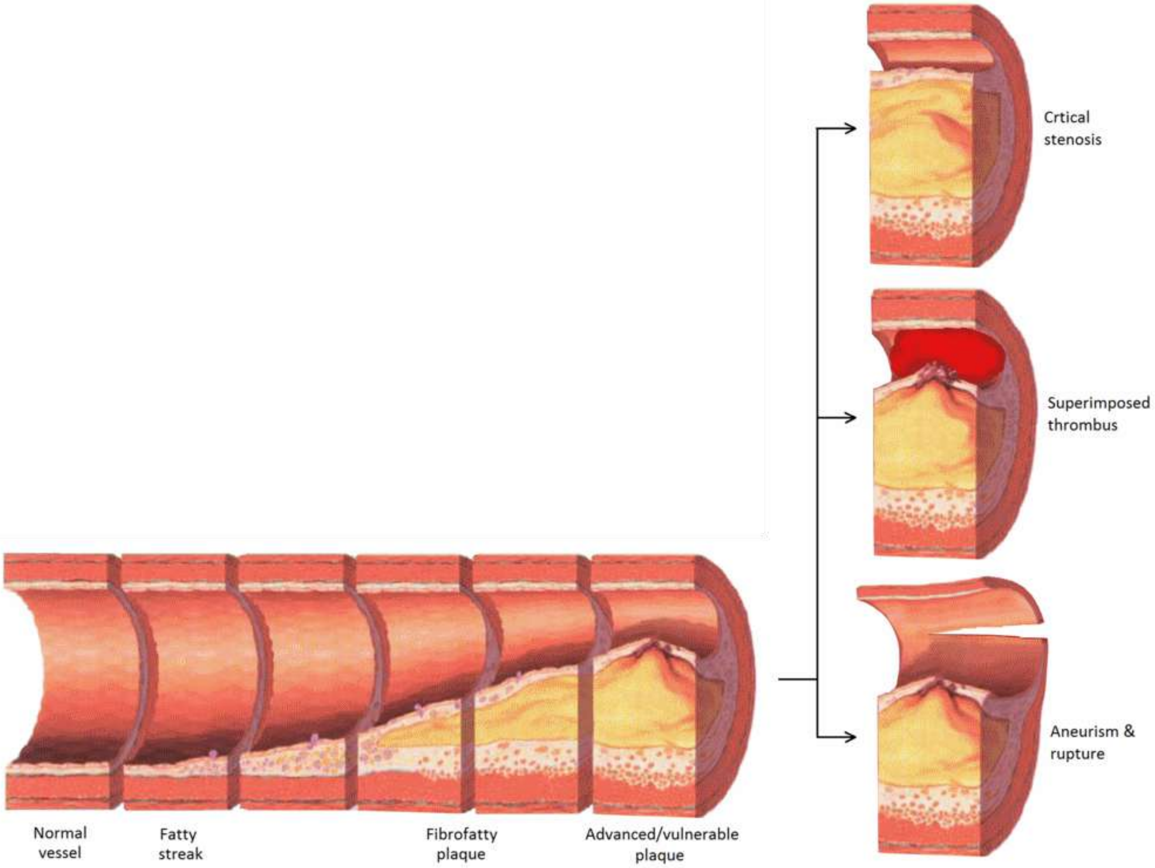
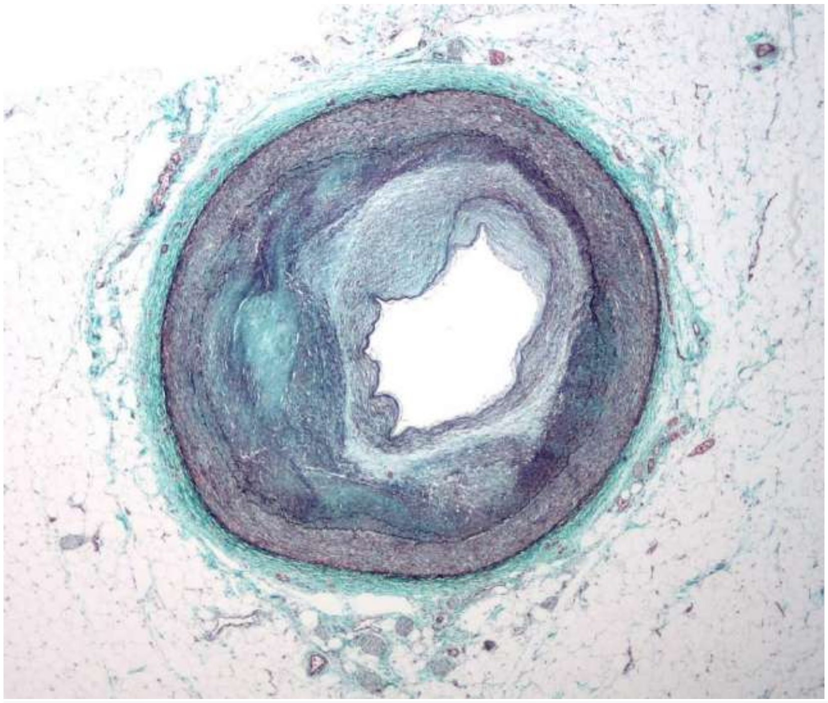

Crtical
stenosis
Superimposed
thrombus
Aneurism &
rupture
Normal
vessel
Fatty
streak
Fibrofatty
plaque
Advanced/vulnerable
plaque

Diagram showing the progression of atherosclerosis in the coronary arteries with associated complications on the right.

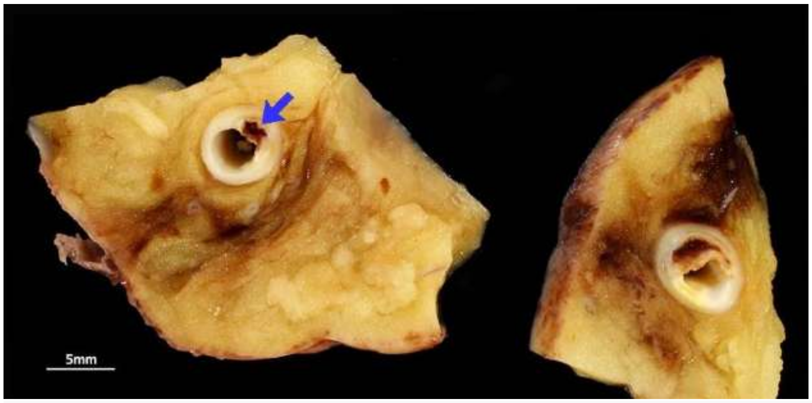


Slide showing a markedly narrowed coronary artery secondary to atherosclerosis. Stained with Masson's trichrome.

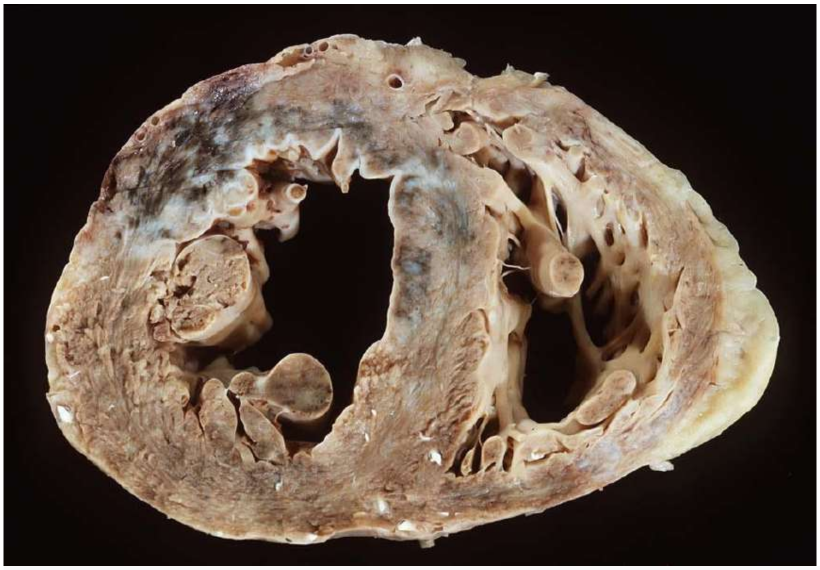
## Complications of atherosclerosis

Once a plaque has formed a number of complications can develop:

- the plaque forms a physical blockage in the lumen of the coronary artery. This may cause reduced blood flow and hence oxygen to the myocardium, particularly at times of increased demand, resulting clinically in angina
- the plaque may rupture, potentially causing a complete occlusion of the coronary artery. This may result in a myocardial infarction



Ruptured coronary artery plaque resulting in thrombosis and associated myocardial infarction.



Pathological specimen showing infarction of the anteroseptal and lateral wall of the left ventricle. There is a background of biventricular myocardial hypertrophy.

## Symptoms and signs

The classic and most common feature of ACS is chest pain.

- typically central/left-sided
- may radiate to the jaw or the left arm
- often described as 'heavy' or constricting, 'like an elephant on my chest'

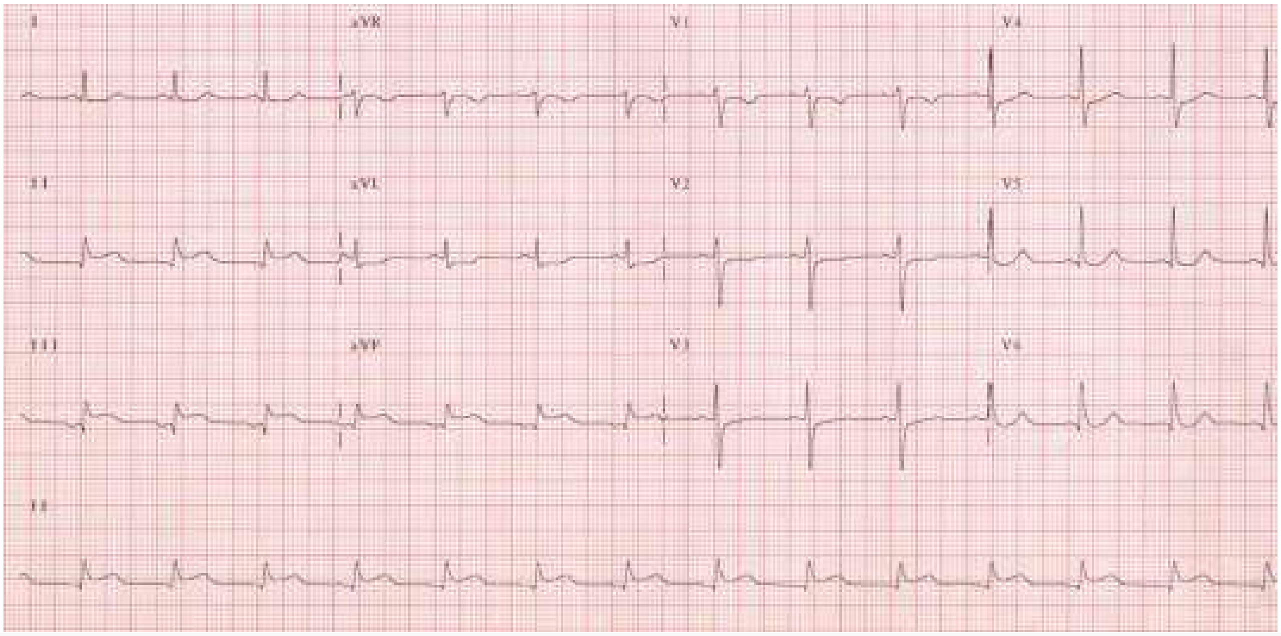
- it should be noted however in real clinical practice patients present with a wide variety of types of chest pain and patients/doctors may confuse ischaemic pain for other causes such as dyspepsia
- certain patients e.g. diabetics/elderly may not experience any chest pain

Other symptoms in ACS include
- dyspnoea
- sweating
- nausea and vomiting

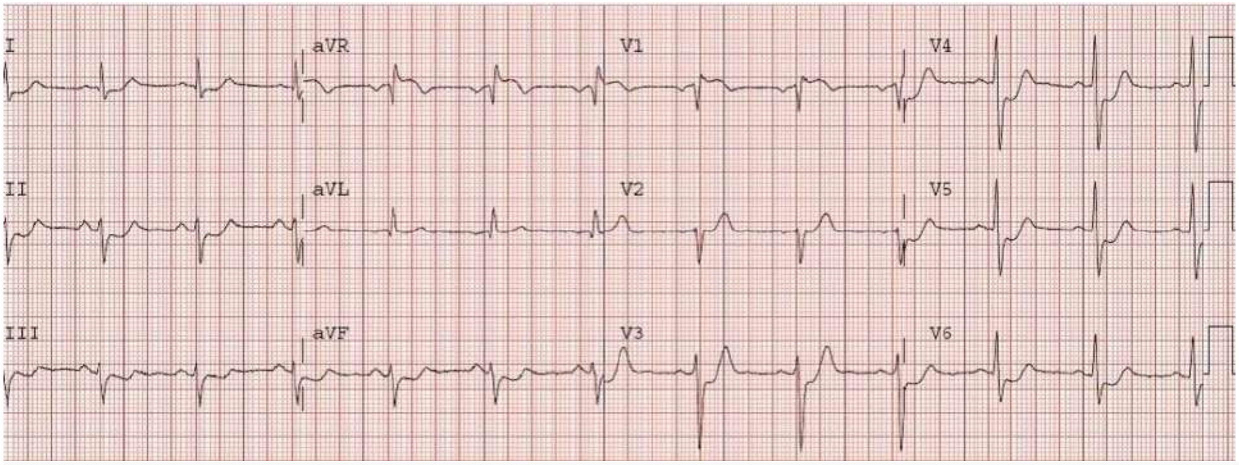
Patients presenting with ACS often have very few physical signs to ellicit:
- pulse, blood pressure, temperature and oxygen saturations are often normal or only mildly altered e.g. tachycardia
- if complications of the ACS have developed e.g. cardiac failure then clearly there may a number of findings
- the patient may appear pale and clammy

**Investigations**

The two most important investigations when assessing a patient with chest pain are:
- ECG
- cardiac markers e.g. troponin



ECG showing a ST elevation myocardial infarction (STEMI). Note by how looking at which leads are affected (in this case II, III and aVF) we are able to tell which coronary arteries are blocked (the right coronary artery in this case). A blockage of the left anterior descending (LAD) artery would cause elevation of V1-V4, what is often termed an 'anterior' myocardial infarction.


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

ECG showing a non-ST elevation myocardial infarction (NSTEMI). On the ECG there is deep ST depression in I-III, aVF, and V3-V6. aVR also has ST elevation. Deep and widespread ST depression is associated with very high mortality because it signifies severe ischemia usually of LAD or left main stem.

The table below shows a simplified correlation between ECG changes and coronary territories:

| | ECG changes | Coronary artery |
|---|---|---|
| **Anterior** | V1-V4 | Left anterior descending |
| **Inferior** | II, III, aVF | Right coronary |
| **Lateral** | I, V5-6 | Left circumflex |

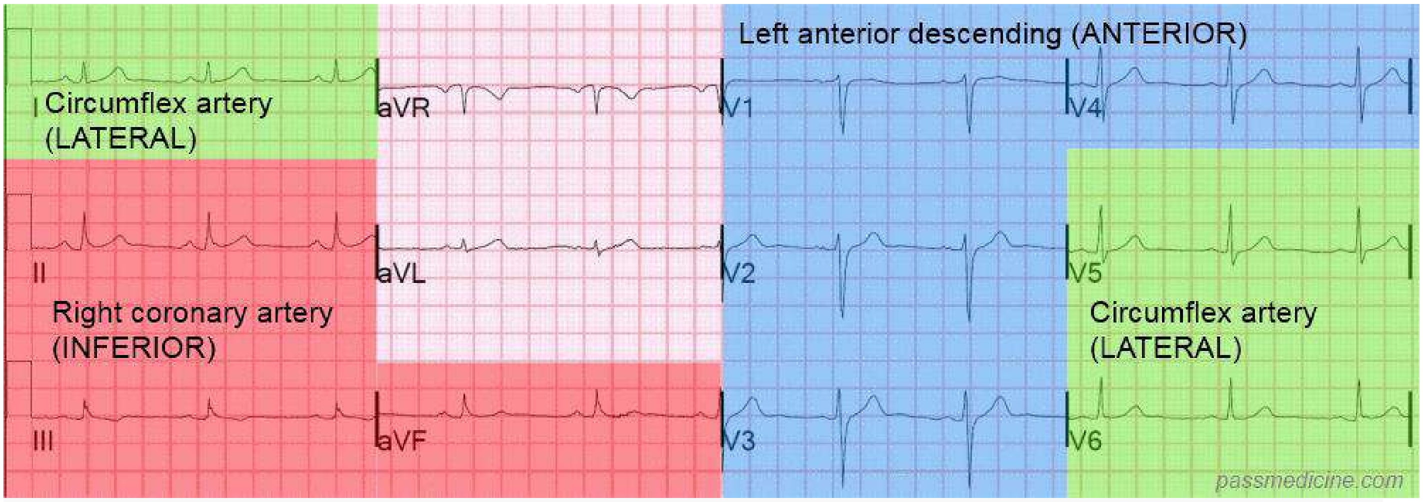

I
Circumflex artery (LATERAL)
aVR
Left anterior descending (ANTERIOR)
V1
V4
II
Right coronary artery (INFERIOR)
aVL
V2
V5
Circumflex artery (LATERAL)
III
aVF
V3
V6
passmedicine.com

Diagram showing the correlation between ECG changes and coronary territories in acute coronary syndrome

## Management

Once a diagnosis of ACS has been made there are a number of elements to treatment:

- prevent worsening of presentation (i.e. further occlusion of coronary vessel)
- revascularise (i.e. 'unblock') the vessel if occluded (patients presenting with a STEMI)
- treat pain

A commonly taught mnemonic for the treatment of ACS is MONA:

- Morphine
- Oxygen
- Nitrates
- Aspirin

Whilst useful it should be remember that not all patients require oxygen therapy. British Thoracic Society guidelines are now widely adopted and oxygen should only be given if the oxygen saturations are < 94%.

For patients who've had a **STEMI** (i.e. one of the coronary arteries has become occluded) the priority of management is to reopen, or revascularise, the blocked vessel.

- a second antiplatelet drug should be given in addition to aspirin. Options include clopidogrel, prasugrel and ticagrelor
- for many years the treatment of choice was thrombolysis. This involved the intravenous administration of a thrombolytic or 'clot-busting' drug to breakdown the thrombus blocking the coronary artery
- since the early 2000's thrombolysis has been superseded by percutaneous coronary intervention (PCI). In this procedure the blocked arteries are opened up using a balloon (angioplasty) following which a stent may be deployed to prevent the artery occluding again in the future. This is done via a catheter inserted into either the radial or femoral artery

If a patient presents with an **NSTEMI** then a risk stratification too (such as GRACE) is used to decide upon further management. If a patient is considered high-risk or is clinically unstable then coronary angiography will be performed during the admission. Lower risk patients may have a coronary angiogram at a later date.

**Secondary prevention**

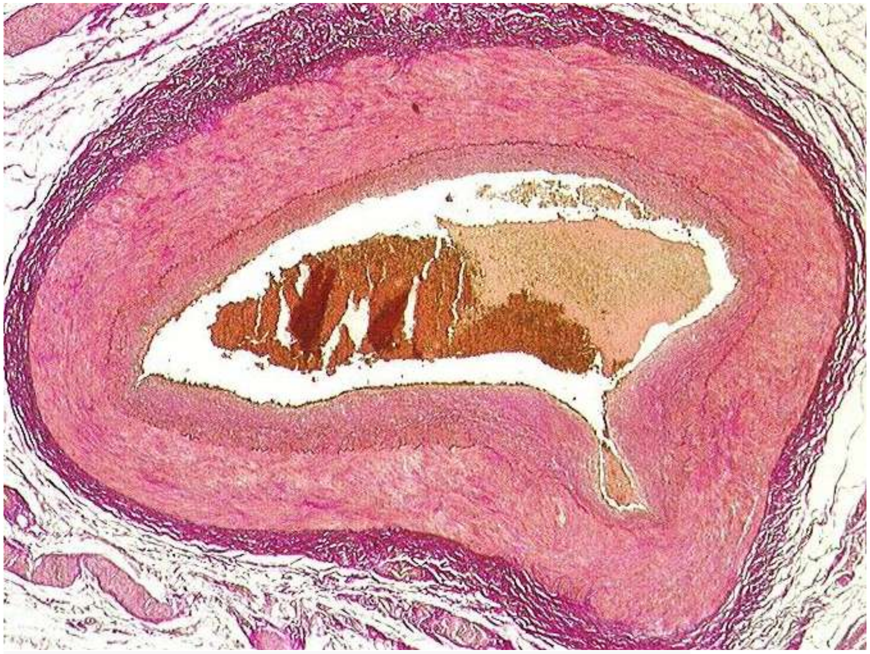
Patients who've had an ACS require lifelong drug therapy to help reduce the risk of a further event. Standard therapy comprises the following as a minimum:

- aspirin
- a second antiplatelet if appropriate (e.g. clopidogrel)

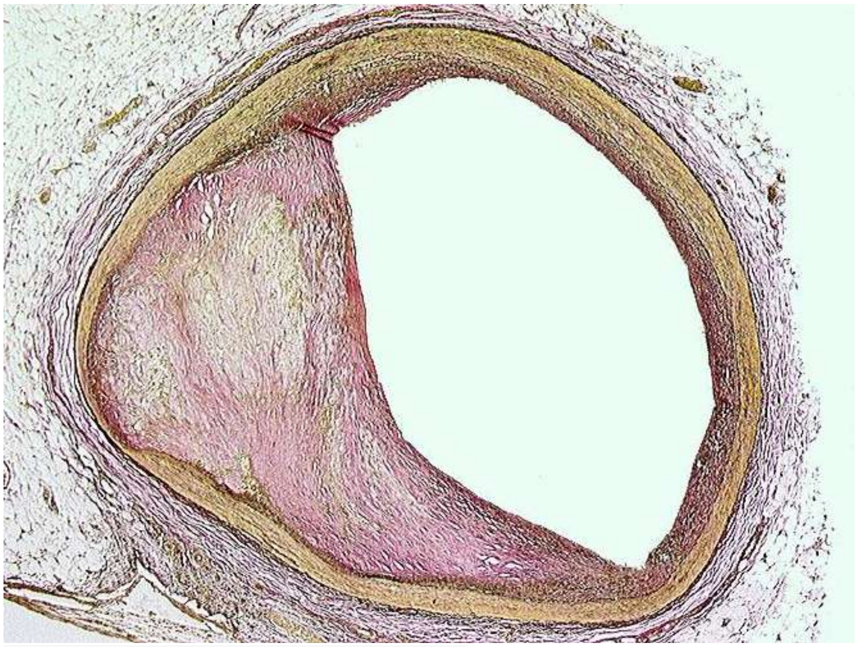
- a beta-blocker
- an ACE inhibitor
- a statin

**Further images**

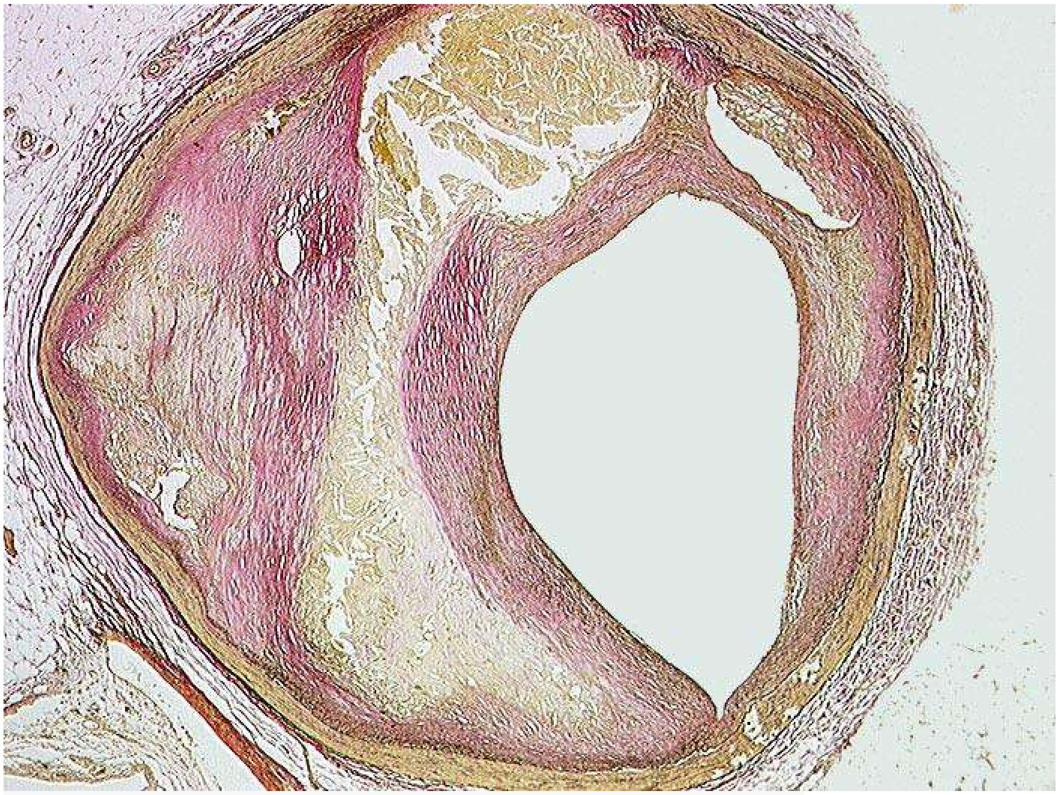
The following images show the progress of coronary artery atherosclerosis:



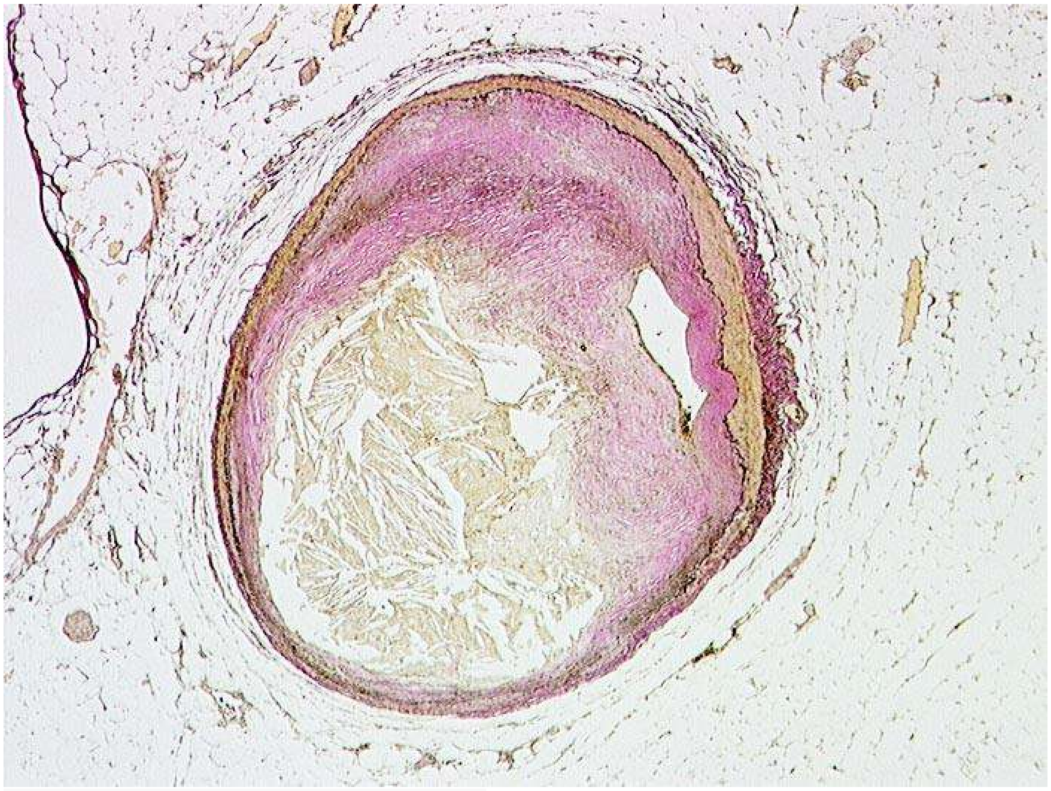
Normal coronary artery with blood in the lumen.



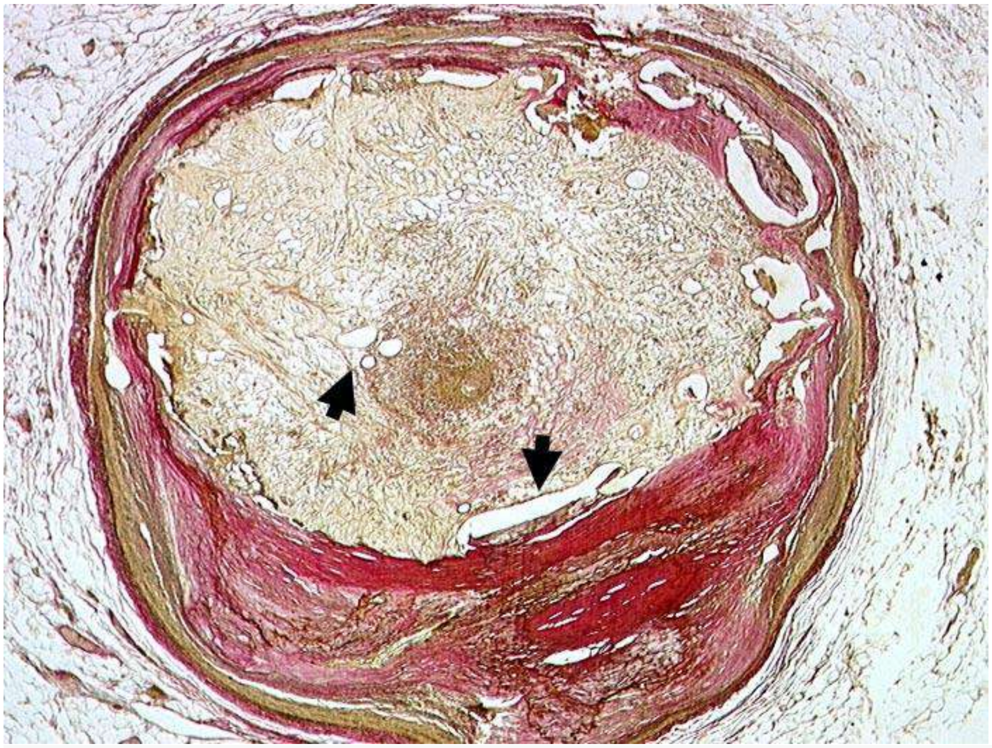
Slightly stenosed coronary artery



Moderately stenosed coronary artery, beetween 50-75%



Severely stenosed coronary artery



Recanalised old atherothrombotic occlusion of a coronary artery. Numerous small neolumina recanalising the organised occluding thrombus (indicated with arrows)

## CARDIAC ENZYMES AND PROTEIN MARKERS

Interpretation of the various cardiac enzymes has now largely been superceded by the introduction of troponin T and I. Questions still however commonly appear in exams.

Key points for the exam

- myoglobin is the first to rise
- CK-MB is useful to look for reinfarction as it returns to normal after 2-3 days (troponin T remains elevated for up to 10 days)

| | Begins to rise | Peak value | Returns to normal |
|---|---|---|---|
| **Myoglobin** | 1-2 hours | 6-8 hours | 1-2 days |
| **CK-MB** | 2-6 hours | 16-20 hours | 2-3 days |
| **CK** | 4-8 hours | 16-24 hours | 3-4 days |
| **Trop T** | 4-6 hours | 12-24 hours | 7-10 days |
| **AST** | 12-24 hours | 36-48 hours | 3-4 days |
| **LDH** | 24-48 hours | 72 hours | 8-10 days |

# ACUTE CORONARY SYNDROME: MANAGEMENT OF NSTEMI

NICE produced guidelines in 2013 on the Secondary prevention in primary and secondary care for patients following a myocardial infarction management of unstable angina and non-ST elevation myocardial infarction (NSTEMI). These superceded the 2010 guidelines which advocated a risk-based approach to management which determined whether drugs such as clopidogrel were given.

All patients should receive
- aspirin 300mg
- nitrates or morphine to relieve chest pain if required

Whilst it is common that non-hypoxic patients receive oxygen therapy there is little evidence to support this approach. The 2008 British Thoracic Society oxygen therapy guidelines advise not giving oxygen unless the patient is hypoxic.

**Antithrombin** treatment. Fondaparinux should be offered to patients who are not at a high risk of bleeding and who are not having angiography within the next 24 hours. If angiography is likely within 24 hours or a patients creatinine is > 265 µmol/l unfractionated heparin should be given.

**Ticagrelor** and **prasugrel** are now the preferred second antiplatelet instead of clopidogrel. **Prasugrel** is generally favoured if the patient is going to have a percutaneous coronary intervention. They should generally be given to all patients and continued for 12 months, although this may vary according to bleeding and ischaemic risk.

**Intravenous glycoprotein IIb/IIIa receptor antagonists** (eptifibatide or tirofiban) should be given to patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%), and who are scheduled to undergo angiography within 96 hours of hospital admission.

**Coronary angiography** should be considered within 96 hours of first admission to hospital to patients who have a predicted 6-month mortality above 3.0%. It should also be performed as soon as possible in patients who are clinically unstable.

The table below summaries the mechanism of action of drugs commonly used in the management of acute coronary syndrome:

| Medication | Mechanism of action |
|---|---|
| **Aspirin** | Antiplatelet - inhibits the production of thromboxane A2 |
| **Clopidogrel** | Antiplatelet - inhibits ADP binding to its platelet receptor |
| **Enoxaparin** | Activates antithrombin III, which in turn potentiates the inhibition of coagulation factors Xa |
| **Fondaparinux** | Activates antithrombin III, which in turn potentiates the inhibition of coagulation factors Xa |
| **Bivalirudin** | Reversible direct thrombin inhibitor |
| **Abciximab, eptifibatide, tirofiban** | Glycoprotein IIb/IIIa receptor antagonists |

# BIVALIRUDIN

Bivalirudin is a reversible direct thrombin inhibitor used as an anticoagulant in the management of acute coronary syndrome.

# ACUTE CORONARY SYNDROME: MANAGEMENT OF STEMI

The management of ST elevation myocardial infarction (STEMI) has changed substantially over the past decade with the widespread adoption of percutaneous coronary intervention (PCI) as the first-line management to revascularise the myocardium.

NICE released guidelines on the management of STEMI in 2013. These guidelines reiterate the need to offer primary PCI to patients who present within 12 hours of onset of symptoms, if it can be delivered within 120 minutes of the time when fibrinolysis could have been given.

A practical example may be a patient who presents with a STEMI to a small district general hospital (DGH) which does not have facilities for PCI. If they cannot be transferred to a larger hospital for PCI within 120 minutes then fibrinolysis should be given. If the patient's ECG taken 90 minutes after fibrinolysis failed to show resolution of the ST elevation then they would then require transfer for PCI.

**Management of STEMI**
The 2008 British Thoracic Society oxygen therapy guidelines have now been widely adopted and oxygen should only be given if the oxygen saturations are < 94%

Sublingual glyceryl trinitrate and intravenous morphine + metoclopramide should be given to help relieve the symptoms.

Aspirin 300mg should be given to all patients (unless contraindicated).

**Following these initial steps there is a large amount of variation in practice in terms of which other medications are given prior to PCI**. A second antiplatelet is normally given, usually ticagrelor, clopidogrel or prasurgel (all are antagonists of the P2Y12 adenosine diphosphate receptor).

Other treatments that may be given include bivalirudin (a direct thrombin inhibitor, usually given alongside aspirin + clopidogrel) and a form of heparin (either low-molecular weight or unfractionated).

→ cath lab for primary PCI

## ACUTE CORONARY SYNDROME: PROGNOSTIC FACTORS

The 2006 Global Registry of Acute Coronary Events (GRACE) study has been used to derive regression models to predict death in hospital and death after discharge in patients with acute coronary syndrome

Poor prognostic factors
- age
- development (or history) of heart failure
- peripheral vascular disease
- reduced systolic blood pressure
- Killip class*
- initial serum creatinine concentration

- elevated initial cardiac markers
- cardiac arrest on admission
- ST segment deviation

***Killip class** - system used to stratify risk post myocardial infarction

| Killip class | Features | 30 day mortality |
|---|---|---|
| I | No clinical signs heart failure | 6% |
| II | Lung crackles, S3 | 17% |
| III | Frank pulmonary oedema | 38% |
| IV | Cardiogenic shock | 81% |

# ANGINA PECTORIS: DRUG MANAGEMENT

The management of stable angina comprises lifestyle changes, medication, percutaneous coronary intervention and surgery. NICE produced guidelines in 2011 covering the management of stable angina

Medication
- all patients should receive aspirin and a statin in the absence of any contraindication
- sublingual glyceryl trinitrate to abort angina attacks
- NICE recommend using either a beta-blocker or a calicum channel blocker first-line based on 'comorbidities, contraindications and the person's preference'
- if a calcium channel blocker is used as monotherapy a rate-limiting one such as verapamil or diltiazem should be used. If used in combination with a beta-blocker then use a long-acting dihydropyridine calcium-channel blocker (e.g. modified-release nifedipine). Remember that beta-blockers should not be prescribed concurrently with verapamil (risk of complete heart block)
- if there is a poor response to initial treatment then medication should be increased to the maximum tolerated dose (e.g. for atenolol 100mg od)
- if a patient is still symptomatic after monotherapy with a beta-blocker add a calcium channel blocker and vice versa
- if a patient is on monotherapy and cannot tolerate the addition of a calcium channel blocker or a beta-blocker then consider one of the following drugs: a long-acting nitrate, ivabradine, nicorandil or ranolazine

- if a patient is taking both a beta-blocker and a calcium-channel blocker then only add a third drug whilst a patient is awaiting assessment for PCI or CABG

Nitrate tolerance

- many patients who take nitrates develop tolerance and experience reduced efficacy
- the BNF advises that patients who develop tolerance should take the second dose of isosorbide mononitrate after 8 hours, rather than after 12 hours. This allows blood-nitrate levels to fall for 4 hours and maintains effectiveness
- this effect is not seen in patients who take modified release isosorbide mononitrate

## NITRATES

Nitrates are a group of drugs which have vasodilating effects. The main indications for their use is in the management of angina and the acute treatment of heart failure. Sublingual glyceryl trinitrate is the most common drug used in patients with ischaemic heart disease to relieve angina attacks.

Mechanism of action

- nitrates cause the release of nitric oxide in smooth muscle, activating guanylate cyclase which then converts GTP to cGMP, which in turn leads to a fall in intracellular calcium levels
- in angina they both dilate the coronary arteries and also reduce venous return which in turn reduces left ventricular work, reducing myocardial oxygen demand

Side-effects

- hypotension
- tachycardia
- headaches
- flushing

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## NICORANDIL

Nicorandil is a vasodilatory drug used to treat angina. It is a potassium-channel activator with vasodilation is through activation of guanylyl cyclase which results in increase cGMP.

Adverse effects
- headache
- flushing
- anal ulceration

Contraindications
- left ventricular failure

## IVABRADINE

Ivabradine is a class of anti-anginal drug which works by reducing the heart rate. It acts on the If ('funny') ion current which is highly expressed in the sinoatrial node, reducing cardiac pacemaker activity.

Adverse effects
- visual effects, particular luminous phenomena, are common
- headache
- bradycardia, heart block

There is no evidence currently of superiority over existing treatments of stable angina.

## MYOCARDIAL INFARCTION: STEMI MANAGEMENT

A number of studies over the past 10 years have provided an evidence for the management of ST-elevation myocardial infarction (STEMI)

In the absence of contraindications, all patients should be given

- **aspirin**
- **P2Y12-receptor antagonist**. Clopidogrel was the first P2Y12-receptor antagonist to be widely used but now ticagrelor is often favoured as studies have shown improved outcomes compared to clopidogrel, but at the expense of slightly higher rates of bleeding. This approached is supported in SIGN's 2016 guidelines. They also recommend that prasugrel (another P2Y12-receptor antagonist) could be considered if the patient is going to have a percutaneous coronary intervention
- **unfractionated heparin** is usually given for patients who're are going to have a PCI. Alternatives include low-molecular weight heparin

NICE suggest the following in terms of oxygen therapy:

- do not routinely administer oxygen, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:
- people with oxygen saturation (SpO2) of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO2 of 94-98%
- people with chronic obstructive pulmonary disease who are at risk of hypercapnic respiratory failure, to achieve a target SpO2 of 88-92% until blood gas analysis is available.

Primary percutaneous coronary intervention (PCI) has emerged as the gold-standard treatment for STEMI but is not available in all centres. Thrombolysis should be performed in patients without access to primary PCI

With regards to thrombolysis:

- tissue plasminogen activator (tPA) has been shown to offer clear mortality benefits over streptokinase
- tenecteplase is easier to administer and has been shown to have non-inferior efficacy to alteplase with a similar adverse effect profile

An ECG should be performed 90 minutes following thrombolysis to assess whether there has been a greater than 50% resolution in the ST elevation

- if there has not been adequate resolution then rescue PCI is superior to repeat thrombolysis
- for patients successfully treated with thrombolysis PCI has been shown to be beneficial. The optimal timing of this is still under investigation

Glycaemic control in patients with diabetes mellitus

- in 2011 NICE issued guidance on the management of hyperglycaemia in acute coronary syndromes
- it recommends using a dose-adjusted insulin infusion with regular monitoring of blood glucose levels to glucose below 11.0 mmol/l
- intensive insulin therapy (an intravenous infusion of insulin and glucose with or without potassium, sometimes referred to as 'DIGAMI') regimes are not recommended routinely

# PERCUTANEOUS CORONARY INTERVENTION

Percutaneous coronary intervention (PCI) is a technique used to restore myocardial perfusion in patients with ischaemic heart disease, both in patients with stable angina and acute coronary syndromes. Stents are implanted in around 95% of patients - it is now rare for just balloon angioplasty to be performed

Following stent insertion migration and proliferation of smooth muscle cells and fibroblasts occur to the treated segment. The stent struts eventually become covered by endothelium. Until this happens there is an increased risk of platelet aggregation leading to thrombosis.

Two main complications may occur

- stent thrombosis: due to platelet aggregation as above. Occurs in 1-2% of patients, most commonly in the first month. Usually presents with acute myocardial infarction
- restenosis: due to excessive tissue proliferation around stent. Occurs in around 5-20% of patients, most commonly in the first 3-6 months. Usually presents with the recurrence of angina symptoms. Risk factors include diabetes, renal impairment and stents in venous bypass grafts

Types of stent

- bare-metal stent (BMS)
- drug-eluting stents (DES): stent coated with paclitaxel or rapamycin which inhibit local tissue growth. Whilst this reduces restenosis rates the stent thrombosis rates are increased as the process of stent endothelisation is slowed

Following insertion, the most important factor in preventing stent thrombosis is antiplatelet therapy. Aspirin should be continued indefinitely. The length of clopidogrel treatment depends on the type of stent, reason for insertion and consultant preference

## THROMBOLYSIS

Thrombolytic drugs activate plasminogen to form plasmin. This in turn degrades fibrin and help breaks up thrombi. They in primarily used in patients who present with a ST elevation myocardial infarction. Other indications include acute ischaemic stroke and pulmonary embolism, although strict inclusion criteria apply.

Examples
- alteplase
- tenecteplase
- streptokinase

Contraindications to thrombolysis
- active internal bleeding
- recent haemorrhage, trauma or surgery (including dental extraction)
- coagulation and bleeding disorders
- intracranial neoplasm
- stroke < 3 months
- aortic dissection
- recent head injury
- pregnancy
- severe hypertension

Side-effects
- haemorrhage
- hypotension - more common with streptokinase
- allergic reactions may occur with streptokinase

# MYOCARDIAL INFARCTION: COMPLICATIONS

Patients are at risk of a number of immediate, early and late complications following a myocardial infarction (MI).

**Cardiac arrest**

This most commonly occurs due to patients developing ventricular fibrillation and is the most common cause of death following a MI. Patients are managed as per the ALS protocol with defibrillation.

**Cardiogenic shock**

If a large part of the ventricular myocardium is damaged in the infarction the ejection fraction of the heart may decrease to the point that the patient develops cardiogenic shock. This is difficult to treat. Other causes of cardiogenic shock include the 'mechanical' complications such as left ventricular free wall rupture as listed below. Patients may require inotropic support and/or an intra-aortic balloon pump.

**Chronic heart failure**

As described above, if the patient survives the acute phase their ventricular myocardium may be dysfunctional resulting in chronic heart failure. Loop diuretics such as furosemide will decrease fluid overload. Both ACE-inhibitors and beta-blockers have been shown to improve the long-term prognosis of patients with chronic heart failure.

**Tachyarrhythmias**

Ventricular fibrillation, as mentioned above, is the most common cause of death following a MI. Other common arrhythmias including ventricular tachycardia.

**Bradyarrhythmias**

Atrioventricular block is more common following inferior myocardial infarctions.

**Pericarditis**

Pericarditis in the first 48 hours following a transmural MI is common (c. 10% of patients). The pain is typical for pericarditis (worse on lying flat etc), a pericardial rub may be heard and a pericardial effusion may be demonstrated with an echocardiogram.

Dressler's syndrome tends to occur around 2-6 weeks following a MI. The underlying pathophysiology is thought to be an autoimmune reaction against antigenic proteins formed as the myocardium recovers. It is characterised by a combination of fever, pleuritic pain, pericardial effusion and a raised ESR. It is treated with NSAIDs.

**Left ventricular aneurysm**
The ischaemic damage sustained may weaken the myocardium resulting in aneurysm formation. This is typically associated with persistent ST elevation and left ventricular failure. Thrombus may form within the aneurysm increasing the risk of stroke. Patients are therefore anticoagulated.

**Left ventricular free wall rupture**
This is seen in around 3% of MIs and occurs around 1-2 weeks afterwards. Patients present with acute heart failure secondary to cardiac tamponade (raised JVP, pulsus paradoxus, diminished heart sounds). Urgent pericardiocentesis and thoracotomy are required.

**Ventricular septal defect**
Rupture of the interventricular septum usually occurs in the first week and is seen in around 1-2% of patients. Features: acute heart failure associated with a pan-systolic murmur. An echocardiogram is diagnostic and will exclude acute mitral regurgitation which presents in a similar fashion. Urgent surgical correction is needed.

**Acute mitral regurgitation**
More common with infero-posterior infarction and may be due to ischaemia or rupture of the papillary muscle. Acute hypotension and pulmonary oedema may occur. An early-to-mid systolic murmur is typically heard. Patients are treated with vasodilator therapy but often require emergency surgical repair.

# MYOCARDIAL INFARCTION: SECONDARY PREVENTION

NICE produced guidelines on the management of patients following a myocardial infarction (MI) in 2013. Some key points are listed below

All patients should be offered the following drugs:
- dual antiplatelet therapy (aspirin plus a second antiplatelet agent)

- ACE inhibitor
- beta-blocker
- statin

Some selected lifestyle points:

- diet: advise a Mediterranean style diet, switch butter and cheese for plant oil based products. Do not recommend omega-3 supplements or eating oily fish
- exercise: advise 20-30 mins a day until patients are 'slightly breathless'
- sexual activity may resume 4 weeks after an uncomplicated MI. Reassure patients that sex does not increase their likelihood of a further MI. PDE5 inhibitors (e.g, sildenafil) may be used 6 months after a MI. They should however be avoided in patient prescribed either nitrates or nicorandil

Most patients who've had an acute coronary syndrome are now given dual antiplatelet therapy (DAPT). Clopidogrel was previously the second antiplatelet of choice. Now ticagrelor and prasugrel (also ADP-receptor inhibitors) are more widely used. The NICE Clinical Knowledge Summaries now recommend:

- post acute coronary syndrome (medically managed): add ticagrelor to aspirin, stop ticagrelor after 12 months
- post percutaneous coronary intervention: add prasugrel or ticagrelor to aspirin, stop the second antiplatelet after 12 months
- this 12 month period may be altered for people at a high-risk of bleeding or those who at high-risk of further ischaemic events

Aldosterone antagonists

- patients who have had an acute MI and who have symptoms and/or signs of heart failure and left ventricular systolic dysfunction, treatment with an aldosterone antagonist licensed for post-MI treatment (e.g. eplerenone) should be initiated within 3-14 days of the MI, preferably after ACE inhibitor therapy

# ACUTE PERICARDITIS

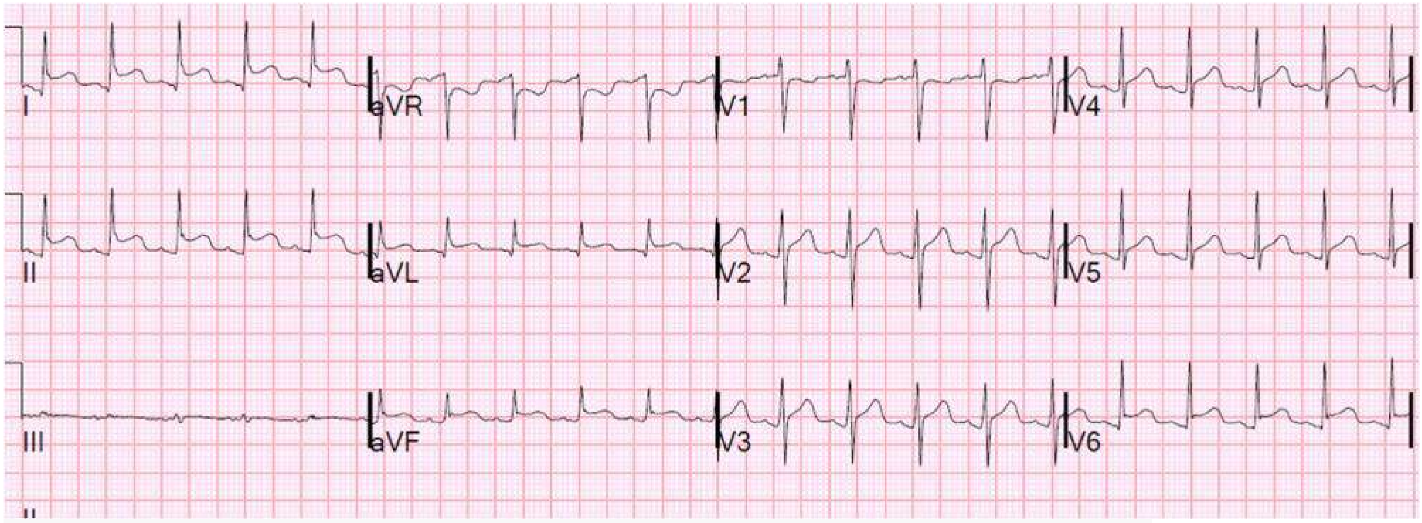
Pericarditis is one of the differentials of any patient presenting with chest pain.

Features
- chest pain: may be pleuritic. Is often relieved by sitting forwards
- other symptoms include non-productive cough, dyspnoea and flu-like symptoms
- pericardial rub
- tachypnoea
- tachycardia

Causes
- viral infections (Coxsackie)
- tuberculosis
- uraemia (causes 'fibrinous' pericarditis)
- trauma
- post-myocardial infarction, Dressler's syndrome
- connective tissue disease
- hypothyroidism
- malignancy

Investigations
- ECG changes
- the changes in pericarditis are often global/widespread, as opposed to the 'territories' seen in ischaemic events
- 'saddle-shaped' ST elevation
- PR depression: most specific ECG marker for pericarditis
- all patients with suspected acute pericarditis should have transthoracic echocardiography

Management
- treat the underlying cause
- a combination of NSAIDs and colchicine is now generally used for first-line for patients with acute idiopathic or viral pericarditis



ECG showing pericarditis. Note the widespread nature of the ST elevation and the PR depression

## CONSTRICTIVE PERICARDITIS

Causes

- any cause of pericarditis
- particularly TB

Features

- dyspnoea
- right heart failure: elevated JVP, ascites, oedema, hepatomegaly
- JVP shows prominent x and y descent
- pericardial knock - loud S3
- Kussmaul's sign is positive

CXR

- pericardial calcification

The key differences between constrictive pericarditis and cardiac tamponade are summarized in the table below:

| | Cardiac tamponade | Constrictive pericarditis |
|---|---|---|
| **JVP** | Absent Y descent | X + Y present |
| **Pulsus paradoxus** | Present | Absent |
| **Kussmaul's sign*** | Rare | Present |
| **Characteristic features** | | Pericardial calcification on CXR |

A commonly used mnemonic to remember the absent Y descent in cardiac tamponade is TAMponade = TAMpaX

*a paradoxical rise in JVP during inspiration

# MYOCARDITIS

Causes

- viral: coxsackie B, HIV
- bacteria: diphtheria, clostridia
- spirochaetes: Lyme disease
- protozoa: Chagas' disease, toxoplasmosis
- autoimmune
- drugs: doxorubicin

Presentation

- usually young patient with an acute history
- chest pain, dyspnoea

Investigations

- raised inflammatory markers in 99%
- ECG: ST/T wave changes including ST-segment elevation and T wave inversion

Complications

- heart failure
- arrhythmia, possibly leading to sudden death
- dilated cardiomyopathy: usually a late complication

# INFECTIVE ENDOCARDITIS

The strongest risk factor for developing infective endocarditis is a previous episode of endocarditis. The following types of patients are affected:

- previously normal valves (50%, typically acute presentation)
  - the mitral valve is most commonly affected
- rheumatic valve disease (30%)
- prosthetic valves
- congenital heart defects
- intravenous drug users (IVDUs, e.g. typically causing tricuspid lesion)
- others: recent piercings

Causes

- historically Streptococcus viridans was the most common cause of infective endocarditis. This is no longer the case, except in developing countries. **Staphylococcus aureus is now the most common cause of infective endocarditis**. Staphylococcus aureus is also particularly common in acute presentation and IVDUs
- coagulase-negative Staphylococci such as Staphylococcus epidermidis commonly colonize indwelling lines and are the most cause of endocarditis in patients following prosthetic valve surgery, usually the result of perioperative contamination. After 2 months the spectrum of organisms which cause endocarditis return to normal (i.e. Staphylococcus aureus is the most common cause)
- Streptococcus viridans still accounts for around 20% of cases. Technically Streptococcus viridans is a pseudotaxonomic term, referring to viridans streptococci, rather than a particular organism. The two most notable viridans streptococci are Streptococcus mitis and Streptococcus sanguinis. They are both commonly found in the mouth and in particular dental plaque so endocarditis caused by these organisms is linked with poor dental hygiene or following a dental procedure
- Streptococcus bovis is associated with colorectal cancer
  - the subtype Streptococcus gallolyticus is most linked with colorectal cancer
- non-infective: systemic lupus erythematosus (Libman-Sacks), malignancy: marantic endocarditis

Culture negative causes

- prior antibiotic therapy
- Coxiella burnetii

- Bartonella
- Brucella
- HACEK: Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella)

*Lancet 2016; 387: 882-93 Infective Endocarditis

# INFECTIVE ENDOCARDITIS: FEATURES

**Modified Duke criteria**
Infective endocarditis diagnosed if

- pathological criteria positive, or
- 2 major criteria, or
- 1 major and 3 minor criteria, or
- 5 minor criteria

**Pathological criteria**
Positive histology or microbiology of pathological material obtained at autopsy or cardiac surgery (valve tissue, vegetations, embolic fragments or intracardiac abscess content)

**Major criteria**
Positive blood cultures

- two positive blood cultures showing typical organisms consistent with infective endocarditis, such as Streptococcus viridans and the HACEK group, or
- persistent bacteraemia from two blood cultures taken > 12 hours apart or three or more positive blood cultures where the pathogen is less specific such as Staph aureus and Staph epidermidis, or
- positive serology for Coxiella burnetii, Bartonella species or Chlamydia psittaci, or
- positive molecular assays for specific gene targets

Evidence of endocardial involvement

- positive echocardiogram (oscillating structures, abscess formation, new valvular regurgitation or dehiscence of prosthetic valves), or
- new valvular regurgitation

**Minor criteria**

- predisposing heart condition or intravenous drug use
- microbiological evidence does not meet major criteria
- fever > 38ºC
- vascular phenomena: major emboli, splenomegaly, clubbing, splinter haemorrhages, Janeway lesions, petechiae or purpura
- immunological phenomena: glomerulonephritis, Osler's nodes, Roth spots

# INFECTIVE ENDOCARDITIS: PROGNOSIS AND MANAGEMENT

Poor prognostic factors

- Staphylococcus aureus infection (see below)
- prosthetic valve (especially 'early', acquired during surgery)
- culture negative endocarditis
- low complement levels

Mortality according to organism

- staphylococci - 30%
- bowel organisms - 15%
- streptococci - 5%

Current antibiotic guidelines (source: British National Formulary)

| **Scenario** | **Suggested antibiotic therapy** |
|---|---|
| Initial blind therapy | Native valve<br>• amoxicillin, consider adding low-dose gentamicin<br>If penicillin allergic, MRSA or severe sepsis<br>• vancomycin + low-dose gentamicin<br>If prosthetic valve |

| Scenario | Suggested antibiotic therapy |
|---|---|
| | - vancomycin + rifampicin + low-dose gentamicin |
| Native valve endocarditis caused by staphylococci | Flucloxacillin<br>If penicillin allergic or MRSA<br>- vancomycin + rifampicin |
| Prosthetic valve endocarditis caused by staphylococci | Flucloxacillin + rifampicin + low-dose gentamicin<br>If penicillin allergic or MRSA<br>- vancomycin + rifampicin + low-dose gentamicin |
| Endocarditis caused by fully-sensitive streptococci (e.g. viridans) | Benzylpenicillin<br>If penicillin allergic<br>- vancomycin + low-dose gentamicin |
| Endocarditis caused by less sensitive streptococci | Benzylpenicillin + low-dose gentamicin<br>If penicillin allergic<br>- vancomycin + low-dose gentamicin |

Indications for surgery

- severe valvular incompetence
- aortic abscess (often indicated by a lengthening PR interval)
- infections resistant to antibiotics/fungal infections
- cardiac failure refractory to standard medical treatment
- recurrent emboli after antibiotic therapy

# INFECTIVE ENDOCARDITIS: PROPHYLAXIS

The 2008 guidelines from NICE have radically changed the list of procedures for which antibiotic prophylaxis is recommended

NICE recommends the following procedures do not require prophylaxis:

- dental procedures
- upper and lower gastrointestinal tract procedures
- genitourinary tract; this includes urological, gynaecological and obstetric procedures and childbirth
- upper and lower respiratory tract; this includes ear, nose and throat procedures and bronchoscopy

The guidelines do however suggest:

- any episodes of infection in people at risk of infective endocarditis should be investigated and treated promptly to reduce the risk of endocarditis developing
- if a person at risk of infective endocarditis is receiving antimicrobial therapy because they are undergoing a gastrointestinal or genitourinary procedure at a site where there is a suspected infection they should be given an antibiotic that covers organisms that cause infective endocarditis

It is important to note that these recommendations are not in keeping with the American Heart Association/European Society of Cardiology guidelines which still advocate antibiotic prophylaxis for high-risk patients who are undergoing dental procedures.

# RHEUMATIC FEVER

Rheumatic fever develops following an immunological reaction to recent (2-6 weeks ago) Streptococcus pyogenes infection.

Pathogenesis
- Streptococcus pyogenes infection → activation of the innate immune system leading to antigen presentation to T cells
- B and T cells produce IgG and IgM antibodies and CD4+ T cells are activated
- there is then a cross-reactive immune response (a form of type II hypersensitivity) thought to be mediated by molecular mimicry
- the cell wall of Streptococcus pyogenes includes M protein, a virulence factor that is highly antigenic. It is thought that the antibodies against M protein cross-react with myosin and the smooth muscle of arteries
- this response leads to the clinical features of rheumatic fever
- Aschoff bodies describes the granulomatous nodules found in rheumatic heart fever

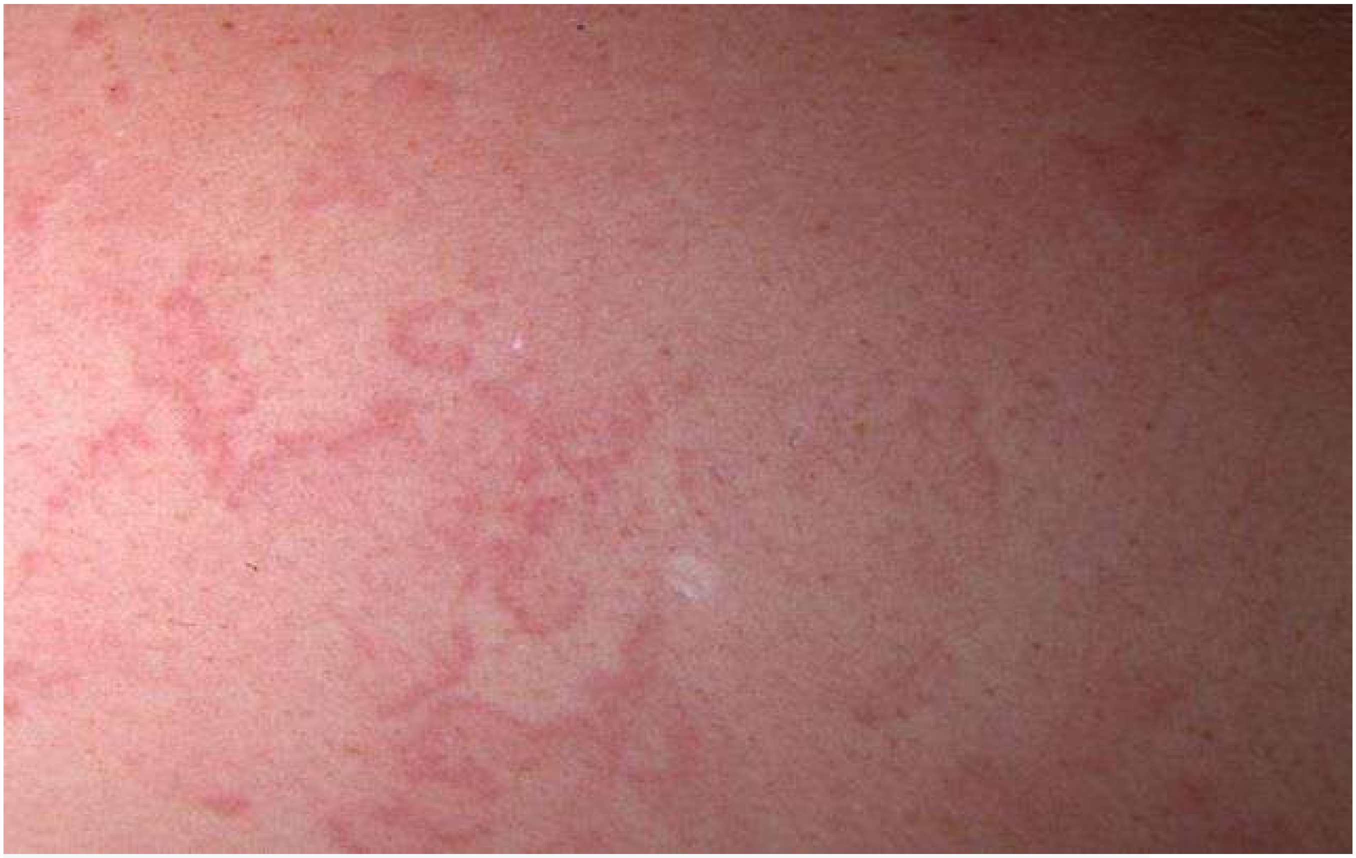
Diagnosis is based on evidence of recent streptococcal infection accompanied by:
- 2 major criteria
- 1 major with 2 minor criteria

Evidence of recent streptococcal infection
- raised or rising streptococci antibodies,
- positive throat swab
- positive rapid group A streptococcal antigen test

Major criteria
- erythema marginatum
- Sydenham's chorea: this is often a late feature
- polyarthritis
- carditis and valvulitis (eg, pancarditis)*
- subcutaneous nodules

Minor criteria
- raised ESR or CRP
- pyrexia
- arthralgia (not if arthritis a major criteria)

- prolonged PR interval



Erythema marginatum is seen in around 10% of children with rheumatic fever. It is rare in adults

*The latest iteration of the Jones criteria (published in 2015) state that rheumatic carditis cannot be based on pericarditis or myocarditis alone and that there must be evidence of endocarditis (the clinical correlate of which is valvulitis which manifests as a regurgitant murmur).

# ADULT ADVANCED LIFE SUPPORT

The following is based on the 2015 Resus Council guidelines. Please see the link for more details, below is only a very brief summary of key points.

Major points include:

- ratio of chest compressions to ventilation is 30:2
- chest compressions are now continued while a defibrillator is charged
- during a VF/VT cardiac arrest, adrenaline 1 mg is given once chest compressions have restarted after the third shock and then every 3-5 minutes (during alternate cycles of CPR).
- a single shock for VF/pulseless VT followed by 2 minutes of CPR, rather than a series of 3 shocks followed by 1 minute of CPR
- if the cardiac arrested is witnessed in a monitored patient (e.g. in a coronary care unit) then the 2015 guidelines recommend 'up to three quick successive (stacked) shocks', rather than 1 shock followed by CPR
- asystole/pulseless-electrical activity: adrenaline 1mg should be given as soon as possible. Should be treated with 2 minutes of CPR prior to reassessment of the rhythm
- atropine is no longer recommended for routine use in asystole or pulseless electrical activity (PEA)
- delivery of drugs via a tracheal tube is no longer recommended
- following successful resuscitation oxygen should be titrated to achieve saturations of 94-98%. This is to address the potential harm caused by hyperoxaemia

Reversible causes of cardiac arrest:

| The 'Hs' | The 'Ts' |
|---|---|
| • Hypoxia<br>• Hypovolaemia<br>• Hyperkalaemia, hypokalaemia, hypoglycaemia, hypocalcaemia, acidaemia and other metabolic disorders<br>• Hypothermia | ⍰ Thrombosis (coronary or pulmonary)<br>⍰ Tension pneumothorax<br>⍰ Tamponade – cardiac<br>⍰ Toxins |

# PERI-ARREST RHYTHMS: BRADYCARDIA

The 2015 Resuscitation Council (UK) guidelines emphasise that the management of bradycardia depends on:
1. identifying the presence of signs indicating haemodynamic compromise - 'adverse signs'
2. identifying the potential risk of asystole

**Adverse signs**
The following factors indicate haemodynamic compromise and hence the need for treatment:

- shock: hypotension (systolic blood pressure < 90 mmHg), pallor, sweating, cold, clammy extremities, confusion or impaired consciousness
- syncope
- myocardial ischaemia
- heart failure

Atropine (500mcg IV) is the first line treatment in this situation.

If there is an unsatisfactory response the following interventions may be used:

- atropine, up to maximum of 3mg
- transcutaneous pacing
- isoprenaline/adrenaline infusion titrated to response

Specialist help should be sought for consideration of transvenous pacing if there is no response to the above measures.

**Potential risk of asystole**
The following are risk factors for asystole. Even if there is a satisfactory response to atropine specialist help is indicated to consider the need for transvenous pacing:

- complete heart block with broad complex QRS
- recent asystole
- Mobitz type II AV block
- ventricular pause > 3 seconds

## PACEMAKERS: TEMPORARY

Indications for a temporary pacemaker
- symptomatic/haemodynamically unstable bradycardia, not responding to atropine
- post-ANTERIOR MI: type 2 or complete heart block*
- trifascicular block prior to surgery

*post-INFERIOR MI complete heart block is common and can be managed conservatively if asymptomatic and haemodynamically stable

## ATROPINE

Atropine is an antagonist of the muscarinic acetylcholine receptor.

Uses*
- treatment of organophosphate poisoning

Physiological effects
- tachycardia
- mydriasis

*atropine is no longer used in resuscitation

## PERI-ARREST RHYTHMS: TACHYCARDIA

The 2015 Resuscitation Council (UK) guidelines have simplified the advice given for the management of peri-arrest tachycardias. Separate algorithms for the management of broad-complex tachycardia, narrow complex tachycardia and atrial fibrillation have been replaced by one unified treatment algorithm

Following basic ABC assessment, patients are classified as being stable or unstable according to the presence of any adverse signs:
- shock: hypotension (systolic blood pressure < 90 mmHg), pallor, sweating, cold, clammy extremities, confusion or impaired consciousness

- syncope
- myocardial ischaemia
- heart failure

If any of the above adverse signs are present then synchronised DC shocks should be given

Treatment following this is given according to whether the QRS complex is narrow or broad and whether the rhythm is regular or irregular. The full treatment algorithm can be found at the Resuscitation Council website, below is a very limited summary:

**Broad-complex tachycardia**

Regular

- assume ventricular tachycardia (unless previously confirmed SVT with bundle branch block)
- loading dose of amiodarone followed by 24 hour infusion

Irregular

  - AF with bundle branch block - treat as for narrow complex tachycardia
  - Polymorphic VT (e.g. Torsade de pointes) - IV magnesium

**Narrow-complex tachycardia**

Regular

- vagal manoeuvres followed by IV adenosine
- if above unsuccessful consider diagnosis of atrial flutter and control rate (e.g. Beta-blockers)

Irregular

- probable atrial fibrillation
- if onset < 48 hr consider electrical or chemical cardioversion
- rate control (e.g. Beta-blocker or digoxin) and anticoagulation

## BROAD COMPLEX TACHYCARDIA

Features suggesting VT rather than SVT with aberrant conduction

- AV dissociation

- fusion or capture beats
- positive QRS concordance in chest leads
- marked left axis deviation
- history of IHD
- lack of response to adenosine or carotid sinus massage
- QRS > 160 ms

# ATRIAL SEPTAL DEFECTS

Atrial septal defects (ASDs) are the most likely congenital heart defect to be found in adulthood. They carry a significant mortality, with 50% of patients being dead at 50 years. Two types of ASDs are recognised, ostium secundum and ostium primum. Ostium secundum are the most common

Features
- ejection systolic murmur, fixed splitting of S2
- embolism may pass from venous system to left side of heart causing a stroke

Ostium secundum (70% of ASDs)
- associated with Holt-Oram syndrome (tri-phalangeal thumbs)
- ECG: RBBB with RAD

Ostium primum
- present earlier than ostium secundum defects
- associated with abnormal AV valves
- ECG: RBBB with LAD, prolonged PR interval

# VENTRICULAR SEPTAL DEFECT

Ventricular septal defects (VSD) are the most common cause of congenital heart disease. They close spontaneously in around 50% of cases. Congenital VSDs are associated with chromosomal disorders (e.g. Down's syndrome, Edward's syndrome, Patau syndrome) and single gene disorders such as Non-congenital causes include post myocardial infarction

Features
- classically a pan-systolic murmur which is louder in smaller defects

Complications
- aortic regurgitation*
- infective endocarditis
- Eisenmenger's complex

- right heart failure
- pulmonary hypertension: pregnancy is contraindicated in women with pulmonary hypertension as it carries a 30-50% risk of mortality

*aortic regurgitation is due to a poorly supported right coronary cusp resulting in cusp prolapse

## AORTIC REGURGITATION

Features
- early diastolic murmur: intensity of the murmur is increased by the handgrip manoeuvre
- collapsing pulse
- wide pulse pressure
- Quincke's sign (nailbed pulsation)
- De Musset's sign (head bobbing)
- mid-diastolic Austin-Flint murmur in severe AR - due to partial closure of the anterior mitral valve cusps caused by the regurgitation streams

Causes (due to valve disease)
- rheumatic fever
- infective endocarditis
- connective tissue diseases e.g. RA/SLE
- bicuspid aortic valve

Causes (due to aortic root disease)
- aortic dissection
- spondylarthropathies (e.g. ankylosing spondylitis)
- hypertension
- syphilis
- Marfan's, Ehler-Danlos syndrome

# AORTIC STENOSIS

Clinical features of symptomatic disease
- chest pain
- dyspnoea
- syncope

An **ejection systolic murmur (ESM)** is classically seen in aortic stenosis. This is decreased following the Valsalva manoeuvre.

Features of severe aortic stenosis
- narrow pulse pressure
- slow rising pulse
- delayed ESM
- soft/absent S2
- S4
- thrill
- duration of murmur
- left ventricular hypertrophy or failure

Causes of aortic stenosis
- degenerative calcification (most common cause in older patients > 65 years)
- bicuspid aortic valve (most common cause in younger patients < 65 years)
- William's syndrome (supravalvular aortic stenosis)
- post-rheumatic disease
- subvalvular: HOCM

Management
- if asymptomatic then observe the patient is general rule
- if symptomatic then valve replacement
- if asymptomatic but valvular gradient > 40 mmHg and with features such as left ventricular systolic dysfunction then consider surgery
- cardiovascular disease may coexist. For this reason an angiogram is often done prior to surgery so that the procedures can be combined
- balloon valvuloplasty is limited to patients with critical aortic stenosis who are not fit for valve replacement

# BICUSPID AORTIC VALVE

Overview

- occurs in 1-2% of the population
- usually asymptomatic in childhood
- the majority eventually develop aortic stenosis or regurgitation
- associated with a left dominant coronary circulation (the posterior descending artery arises from the circumflex instead of the right coronary artery) and Turner's syndrome
- around 5% of patients also have coarctation of the aorta

Complications

- aortic stenosis/regurgitation as above
- higher risk for aortic dissection and aneurysm formation of the ascending aorta

# MITRAL REGURGITATION

Also known as mitral insufficiency, mitral regurgitation (MR) occurs when blood leaks back through the mitral valve on systole. It is the second most common valve disease after aortic stenosis. The mitral valve is located between the left atrium and ventricle, and regurgitation leads to a less efficient heart as less blood is pumped through the body with each contraction. This said, MR is common in otherwise healthy patients to a trivial degree and does not need treatment.

As the degree of regurgitation becomes more severe, the body’s oxygen demands may exceed what the heart can supply and as a result, the myocardium can thicken over time. While this may be benign initially, patients may find themselves increasingly fatigued as a thicker myometrium becomes less efficient, and eventually go into irreversible heart failure.

Risk factors

- Female sex
- Lower body mass
- Age
- Renal dysfunction
- Prior myocardial infarction
- Prior mitral stenosis or valve prolapse
- Collagen disorders e.g. Marfan's Syndrome and Ehlers-Danlos syndrome

Causes

- Following coronary artery disease or post-MI: if the papillary muscles or chordae tendinae are affected by a cardiac insult, mitral valve disease may ensue as a result of damage to its supporting structures.
- Mitral valve prolapse: Occurs when the leaflets of the mitral valve is deformed so the valve does not close properly and allows for backflow. Most patients with this have a trivial degree of mitral regurgitation.
- Infective endocarditis: When vegetations from the organisms colonising the heart grow on the mitral valve, it is prevented from closing properly. Patients with abnormal valves are more likely to develop endocarditis as opposed to their peers.
- Rheumatic fever: While this is uncommon in developed countries, rheumatic fever can cause inflammation of the valves and therefore result in mitral regurgitation.
- Congenital

Symptoms

- Most patients with MR are asymptomatic, and patients suffering from mild to moderate MR may stay largely asymptomatic indefinitely. Symptoms tend to be due to failure of the left ventricle, arrhythmias or pulmonary hypertension. This may present as fatigue, shortness of breath and oedema.

Signs

- The murmur heard on auscultation of the chest is typically a pansystolic murmur described as “blowing”. It is heard best at the apex and radiating into the axilla. S1 may be quiet as a result of incomplete closure of the valve. Severe MR may cause a widely split S2

Investigations

- ECG may show a broad P wave, indicative of atrial enlargement
- Cardiomegaly may be seen on chest x-ray, with an enlarged left atrium and ventricle
- Echocardiography is crucial to diagnosis and to assess severity

Treatment options

- Medical management in acute cases involves nitrates, diuretics, positive inotropes and an intra-aortic balloon pump to increase cardiac output
- If patients are in heart failure, ACE inhibitors may be considered along with beta-blockers and spironolactone
- In acute, severe regurgitation, surgery is indicated

- The evidence for repair over replacement is strong in degenerative regurgitation, and is demonstrated through lower mortality and higher survival rates
- When this is not possible, valve replacement with either an artificial valve or a pig valve is considered

## MITRAL VALVE PROLAPSE

Mitral valve prolapse is common, occurring in around 5-10 % of the population. It is usually idiopathic but may be associated with a wide variety of cardiovascular disease and other conditions

Associations
- congenital heart disease: PDA, ASD
- cardiomyopathy
- Turner's syndrome
- Marfan's syndrome, Fragile X
- osteogenesis imperfecta
- pseudoxanthoma elasticum
- Wolff-Parkinson White syndrome
- long-QT syndrome
- Ehlers-Danlos Syndrome
- polycystic kidney disease

Features
- patients may complain of atypical chest pain or palpitations
- mid-systolic click (occurs later if patient squatting)
- late systolic murmur (longer if patient standing)
- complications: mitral regurgitation, arrhythmias (including long QT), emboli, sudden death

## MITRAL STENOSIS

It is said that the causes of mitral stenosis are rheumatic fever, rheumatic fever and rheumatic fever. Rarer causes that may be seen in the exam include mucopolysaccharidoses, carcinoid and endocardial fibroelastosis

Features

- mid-late diastolic murmur (best heard in expiration)
- loud S1, opening snap
- low volume pulse
- malar flush
- atrial fibrillation

Features of severe MS

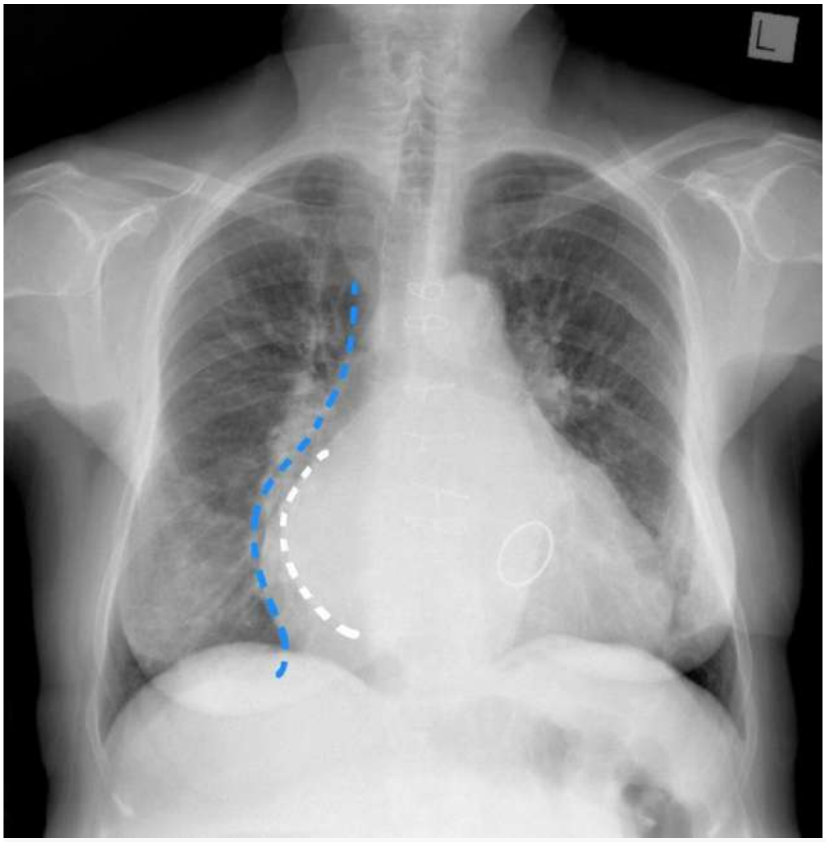
- length of murmur increases
- opening snap becomes closer to S2

Chest x-ray

- left atrial enlargement may be seen

Echocardiography

- the normal cross sectional area of the mitral valve is 4-6 sq cm. A 'tight' mitral stenosis implies a cross sectional area of < 1 sq cm



Chest x-ray from a patient with mitral stenosis. This patient has had a sternotomy and a prosthetic mitral valve. There is splaying of the carina with elevation of the left main bronchus, a double right heart border and cardiomegaly. The features are those of left atrial enlargement. Although the entire heart is enlarged, a double contour is seen through the right side of the heart. The more medial line is the enlarged left atrium (white dotted line) and the heart heart border is more lateral (blue dotted line).

# TRICUSPID REGURGITATION

Signs

- pan-systolic murmur
- prominent/giant V waves in JVP
- pulsatile hepatomegaly
- left parasternal heave

Causes

- right ventricular infarction
- pulmonary hypertension e.g. COPD
- rheumatic heart disease
- infective endocarditis (especially intravenous drug users)
- Ebstein's anomaly
- carcinoid syndrome

# PROSTHETIC HEART VALVES

The most common valves which need replacing are the aortic and mitral valve. There are two main options for replacement: biological (bioprosthetic) or mechanical.

| Biological (bioprosthetic) valves | Mechanical valves |
|---|---|
| Usually bovine or porcine in origin<br>Major disadvantage is structural deterioration and calcification over time. Most older patients ( > 65 years for aortic valves and > 70 years for mitral valves) receive a bioprosthetic valve<br>Long-term anticoagulation not usually needed. Warfarin may be given for the first 3 months depending on patient factors. Low-dose aspirin is given long-term. | The most common type now implanted is the bileaflet valve. Ball-and-cage valves are rarely used nowadays<br>Mechanical valves have a low failure rate<br>Major disadvantage is the increased risk of thrombosis meaning long-term anticoagulation is needed. Following the 2017 European Society of Cardiology guidelines, aspirin is only normally given in addition if there is an additional indication, e.g. ischaemic heart disease.<br>Target INR |

| Biological (bioprosthetic) valves | Mechanical valves |
|---|---|
|  | • aortic: 3.0<br>• mitral: 3.5 |

Following the 2008 NICE guidelines for prophylaxis of endocarditis antibiotics are no longer recommended for common procedures such as dental work.

# PATENT FORAMEN OVALE

Patent foramen ovale (PFO) is present in around 20% of the population. It may allow embolus (e.g. from DVT) to pass from right side of the heart to the left side leading to a stroke - 'a paradoxical embolus'

There also appears to be an association between migraine and PFO. Some studies have reported improvement in migraine symptoms following closure of the PFO.

The management of patients with PFO who've had a stroke remains controversial. Options include antiplatelet therapy, anticoagulant therapy or PFO closure.

# EISENMENGER'S SYNDROME

Eisenmenger's syndrome describes the reversal of a left-to-right shunt in a congenital heart defect due to pulmonary hypertension. This occurs when an uncorrected left-to-right leads to remodeling of the pulmonary microvasculature, eventually causing obstruction to pulmonary blood and pulmonary hypertension.

Associated with
- ventricular septal defect
- atrial septal defect
- patent ductus arteriosus

Features
- original murmur may disappear

- cyanosis
- clubbing
- right ventricular failure
- haemoptysis, embolism

Management

- heart-lung transplantation is required

## CARDIAC CATHETERISATION AND OXYGEN SATURATION LEVELS

Questions regarding cardiac catherisation and oxygen saturation levels can seem daunting at first but a few simple rules combined with logical deduction can usual produce the answer.

Let's start with the basics:

- deoxygenated blood returns to the right side of the heart via the superior vena cava (SVC) and inferior vena cava (IVC). It has an oxygen saturation level of around **70%**. The right atrium (RA), right ventricle (RV) and pulmonary artery (PA) normally have oxygen saturation levels of around 70%
- the lungs oxygenate the blood to a level of around **98-100%**. The left atrium (LA), left ventricle (LV) and aorta should all therefore have oxygen saturation levels of 98-100%

The table below shows the **oxygen saturations** that would be expected in different scenarios:

| **Diagnosis & notes** | **RA** | **RV** | **PA** | **LA** | **LV** | **Aorta** |
|---|---|---|---|---|---|---|
| **Normal** | 70% | 70% | 70% | 100% | 100% | 100% |
| **Atrial septal defect (ASD)**<br><br>The oxygenated blood in the LA mixes with the deoxygenated blood in the RA, resulting in intermediate levels of oxygenation from the RA onwards | 85% | 85% | 85% | 100% | 100% | 100% |
| **Ventricular septal defect (VSD)**<br><br>The oxygenated blood in the LV mixes with the deoxygenated blood in the RV, resulting in intermediate levels of oxygenation from the RV onwards. The RA blood remains deoxygenated | 70% | 85% | 85% | 100% | 100% | 100% |

| Diagnosis & notes | RA | RV | PA | LA | LV | Aorta |
|---|---|---|---|---|---|---|
| **Patent ductus arteriosus (PDA)**<br>Remember, a PDA connects the higher pressure aorta with the lower pressure PA. This results in only the PA having intermediate oxygenation levels | 70% | 70% | 85% | 100% | 100% | 100% |
| **VSD with Eisenmenger's** | 70% | 70% | 70% | 100% | 85% | 85% |
| **PDA with Eisenmenger's** | 70% | 70% | 70% | 100% | 100% | 85% |
| **ASD with Eisenmenger's** | 70% | 70% | 70% | 85% | 85% | 85% |

# BRUGADA SYNDROME

Brugada syndrome is a form of inherited cardiovascular disease with may present with sudden cardiac death. It is inherited in an autosomal dominant fashion and has an estimated prevalence of 1:5,000-10,000. Brugada syndrome is more common in Asians.

Pathophysiology

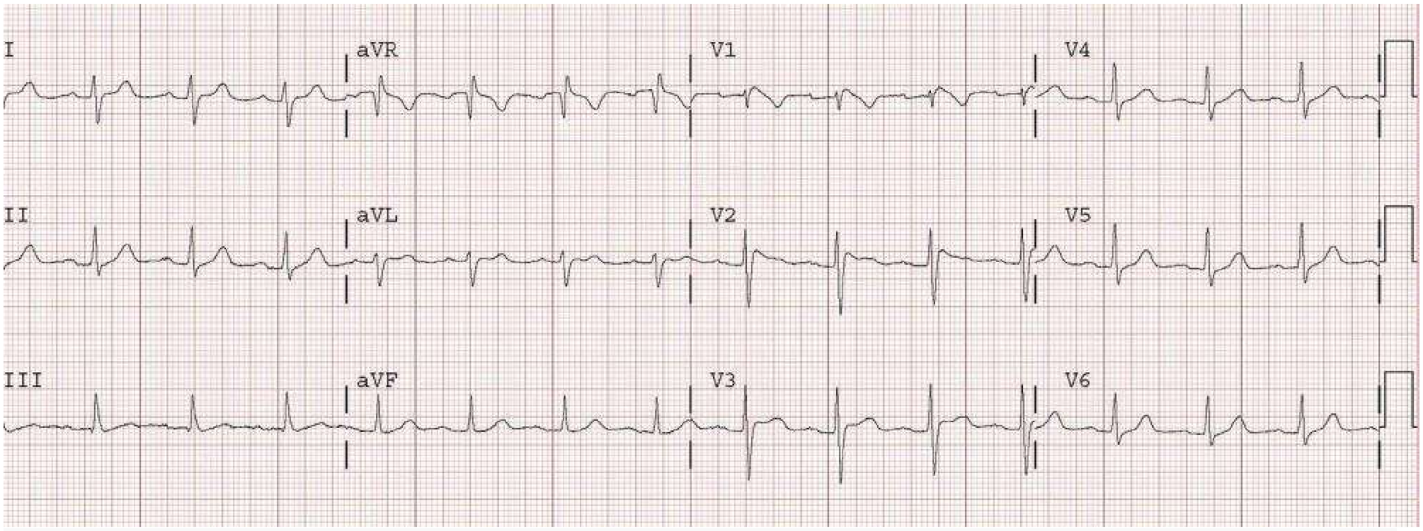
- a large number of variants exist
- around 20-40% of cases are caused by a mutation in the SCN5A gene which encodes the myocardial sodium ion channel protein

ECG changes

- convex ST segment elevation > 2mm in > 1 of V1-V3 followed by a negative T wave
- partial right bundle branch block
- the ECG changes may be more apparent following the administration of flecainide or ajmaline - this is the investigation of choice in suspected cases of Brugada syndrome

Management

- implantable cardioverter-defibrillator



ECG showing Brugada pattern, most marked in V1, which has an incomplete RBBB, a downsloping ST segment and an inverted T wave

# BUERGER'S DISEASE

Buerger's disease (also known as thromboangiitis obliterans) is a small and medium vessel vasculitis that is strongly associated with smoking.

Features

- extremity ischaemia
    - intermittent claudication
    - ischaemic ulcers
- superficial thrombophlebitis
- Raynaud's phenomenon

# CARDIOMYOPATHIES: KEY POINTS

The old classification of dilated, restricted and hypertrophic cardiomyopathy has been largely abandoned due to the high degree of overlap. The latest classification of cardiomyopathy by the WHO and American Heart Association reflect this.

The tables below shows a very limited set of exam related facts for the various cardiomyopathies:

**Primary cardiomyopathies** - predominately involving the heart

**Genetic** - both conditions listed below are autosomal dominant. An implantable cardioverter-defibrillator is often inserted to reduce the incidence of sudden cardiac death.

| Type of cardiomyopathy | Selected points |
|---|---|
| Hypertrophic obstructive cardiomyopathy | Leading cause of sudden cardiac death in young athletes<br>Usually due to a mutation in the gene encoding β-myosin heavy chain protein<br>Common cause of sudden death<br>Echo findings include MR, systolic anterior motion (SAM) of the anterior mitral valve and asymmetric septal hypertrophy |
| Arrhythmogenic right ventricular dysplasia | Right ventricular myocardium is replaced by fatty and fibrofatty tissue<br>Around 50% of patients have a mutation of one of the several genes which encode components of desmosome<br>ECG abnormalities in V1-3, typically T wave inversion. An epsilon wave is found in about 50% of those with ARV - this is best described as a terminal notch in the QRS complex |

**Mixed** - rather confusingly most of the causes of dilated and restrictive cardiomyopathy are now listed separately in the 'secondary' causes. This category servers as a reminder that many patients will have a genetic predisposition to cardiomyopathy which is then triggered by the secondary process, hence the 'mixed' category

| Type of cardiomyopathy | Selected causes/points |
|---|---|
| Dilated cardiomyopathy | Classic causes include<br>• alcohol |

| Type of cardiomyopathy | Selected causes/points |
|---|---|
|  | - Coxsackie B virus<br>- wet beri beri<br>- doxorubicin |
| Restrictive cardiomyopathy | Classic causes include<br>- amyloidosis<br>- post-radiotherapy<br>- Loeffler's endocarditis |

## Acquired

| Type of cardiomyopathy | Selected points |
|---|---|
| Peripartum cardiomyopathy | Typical develops between last month of pregnancy and 5 months post-partum<br>More common in older women, greater parity and multiple gestations |
| Takotsubo cardiomyopathy | 'Stress'-induced cardiomyopathy e.g. patient just found out family member dies then develops chest pain and features of heart failure<br>Transient, apical ballooning of the myocardium<br>Treatment is supportive |

**Secondary cardiomyopathies**- pathological myocardial involvement as part of a generalized systemic disorder

| Type of cardiomyopathy | Selected causes/points |
|---|---|
| Infective | Coxsackie B virus<br>Chagas disease |
| Infiltrative | Amyloidosis |
| Storage | Haemochromatosis |
| Toxicity | Doxorubicin<br>Alcoholic cardiomyopathy |
| Inflammatory (granulomatous) | Sarcoidosis |
| Endocrine | Diabetes mellitus<br>Thyrotoxicosis<br>Acromegaly |
| Neuromuscular | Friedreich's ataxia<br>Duchenne-Becker muscular dystrophy<br>Myotonic dystrophy |

| Type of cardiomyopathy | Selected causes/points |
|---|---|
| Nutritional deficiencies | Beriberi (thiamine) |
| Autoimmune | Systemic lupus erythematosis |

# DILATED CARDIOMYOPATHY

Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy, accounting for 90% of cases.

Causes:

- idiopathic: the most common cause
- myocarditis: e.g. Coxsackie B, HIV, diphtheria, Chagas disease
- ischaemic heart disease
- peripartum
- hypertension
- iatrogenic: e.g. doxorubicin
- substance abuse: e.g. alcohol, cocaine
- inherited: either a familial genetic predisposition to DCM or a specific syndrome e.g. Duchenne muscular dystrophy
  - around a third of patients with DCM are thought to have a genetic predisposition
  - a large number of heterogeneous defects have been identified
  - the majority of defects are inherited in an autosomal dominant fashion although other patterns of inheritance are seen
- infiltrative e.g. haemochromatosis, sarcoidosis
- + these causes may also lead to restrictive cardiomyopathy
- nutritional e.g. wet beriberi (thiamine deficiency)

Pathophysiology

- dilated heart leading to predominately systolic dysfunction
- all 4 chambers are dilated, but the left ventricle more so than right ventricle
- eccentric hypertrophy (sarcomeres added in series) is seen

Features

- classic findings of heart failure
- systolic murmur: stretching of the valves may result in mitral and tricuspid regurgitation

- S3
- 'balloon' appearance of the heart on the chest x-ray

## RESTRICTIVE CARDIOMYOPATHY

Causes
- amyloidosis (e.g. secondary to myeloma) - most common cause in UK
- haemochromatosis
- post-radiation fibrosis
- Loffler's syndrome: endomyocardial fibrosis with a prominent eosinophilic infiltrate
- endocardial fibroelastosis: thick fibroelastic tissue forms in the endocardium; most commonly seen in young children
- sarcoidosis
- scleroderma

Pathophysiology
- primarily characterized by decreased compliance of the ventricular endomyocardium
- causes predominately diastolic dysfunction

Features
- similar to constrictive pericarditis
- low-voltage ECG

Features suggesting restrictive cardiomyopathy rather than constrictive pericarditis
- prominent apical pulse
- absence of pericardial calcification on CXR
- the heart may be enlarged
- ECG abnormalities e.g. bundle branch block, Q waves

Investigations
- echocardiography
- cardiac MRI

# HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY: FEATURES

Hypertrophic obstructive cardiomyopathy (HOCM) is an autosomal dominant disorder of muscle tissue caused by defects in the genes encoding contractile proteins. The estimated prevalence is 1 in 500. HOCM is important as it is the most common cause of sudden cardiac death in the young.

Pathophysiology
- the most common defects involve a mutation in the gene encoding β-myosin heavy chain protein or myosin-binding protein C
- results in predominantly diastolic dysfunction
  - left ventricle hypertrophy → decreased compliance → decreased cardiac output
- characterized by myofibrillar hypertrophy with chaotic and disorganized fashion myocytes ('disarray') and fibrosis on biopsy

Features
- often asymptomatic
- exertional dyspnoea
- angina
- syncope
  - typically following exercise
  - due to subaortic hypertrophy of the ventricular septum, resulting in functional aortic stenosis
- sudden death (most commonly due to ventricular arrhythmias), arrhythmias, heart failure
- jerky pulse, large 'a' waves, double apex beat
- ejection systolic murmur
  - increases with Valsalva manoeuvre and decreases on squatting
  - hypertrophic cardiomyopathy may impair mitral valve closure, thus causing regurgitation

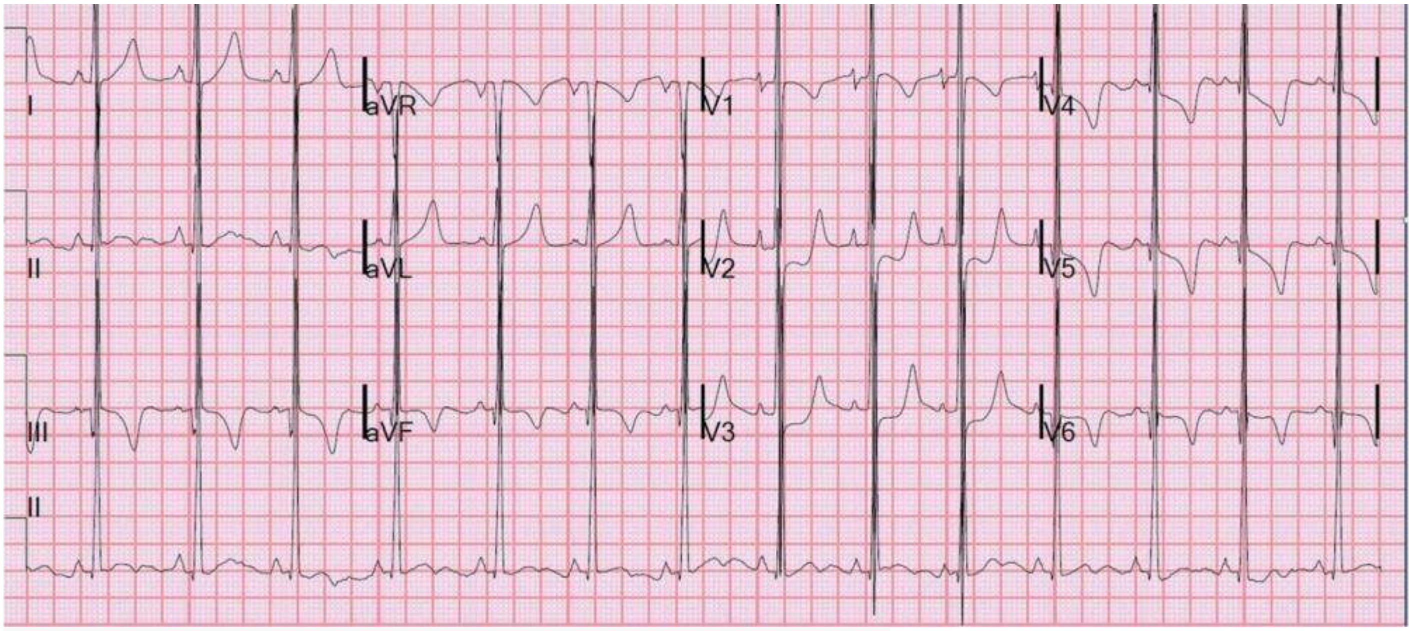
Associations
- Friedreich's ataxia
- Wolff-Parkinson White

Echo findings - mnemonic - MR SAM ASH
- mitral regurgitation (MR)

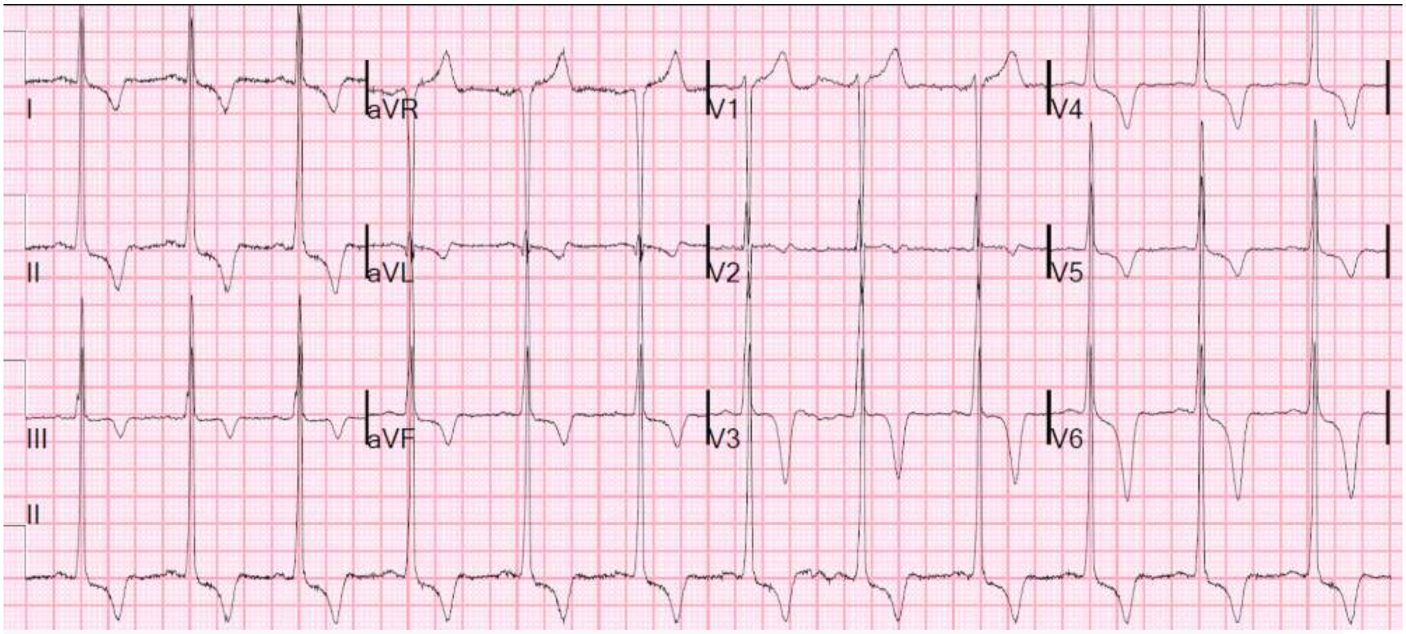
- systolic anterior motion (SAM) of the anterior mitral valve leaflet
- asymmetric hypertrophy (ASH)

ECG

- left ventricular hypertrophy
- non-specific ST segment and T-wave abnormalities, progressive T wave inversion may be seen
- deep Q waves
- atrial fibrillation may occasionally be seen


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

ECG showing typical changes of HOCM including LVH and T wave inversion


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

This young male patient was shown to have HOCM. Note the LVH and deep ST depression and T-wave inversions

# HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY: MANAGEMENT

Hypertrophic obstructive cardiomyopathy (HOCM) is an autosomal dominant disorder of muscle tissue caused by defects in the genes encoding contractile proteins. The estimated prevalence is 1 in 500.

Management
- **A**miodarone
- **B**eta-blockers or verapamil for symptoms
- **C**ardioverter defibrillator
- **D**ual chamber pacemaker
- **E**ndocarditis prophylaxis*

Drugs to avoid
- nitrates
- ACE-inhibitors
- inotropes

*although see the 2008 NICE guidelines on infective endocarditis prophylaxis

# HYPERTROPHIC OBSTRUCTIVE CARDIOMYOPATHY: PROGNOSTIC FACTORS

Hypertrophic obstructive cardiomyopathy (HOCM) is an autosomal dominant disorder of muscle tissue caused by defects in the genes encoding contractile proteins. Mutations to various proteins including beta-myosin, alpha-tropomyosin and troponin T have been identified. Septal hypertrophy causes left ventricular outflow obstruction. It is an important cause of sudden death in apparently healthy individuals.

Poor prognostic factors
- syncope
- family history of sudden death
- young age at presentation
- non-sustained ventricular tachycardia on 24 or 48-hour Holter monitoring

- abnormal blood pressure changes on exercise

An increased septal wall thickness is also associated with a poor prognosis.

## ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC, also known as arrhythmogenic right ventricular dysplasia or ARVD) is a form of inherited cardiovascular disease which may present with syncope or sudden cardiac death. It is generally regarded as the second most common cause of sudden cardiac death in the young after hypertrophic cardiomyopathy.

Pathophysiology
- inherited in an autosomal dominant pattern with variable expression
- the right ventricular myocardium is replaced by fatty and fibrofatty tissue
- around 50% of patients have a mutation of one of the several genes which encode components of desmosome

Presentation
- palpitations
- syncope
- sudden cardiac death

Investigation
- ECG abnormalities in V1-3, typically T wave inversion. An epsilon wave is found in about 50% of those with ARV - this is best described as a terminal notch in the QRS complex
- echo changes are often subtle in the early stages but may show an enlarged, hypokinetic right ventricle with a thin free wall
- magnetic resonance imaging is useful to show fibrofatty tissue

Management
- drugs: sotalol is the most widely used antiarrhythmic
- catheter ablation to prevent ventricular tachycardia
- implantable cardioverter-defibrillator

Naxos disease

- an autosomal recessive variant of ARVC
- a triad of ARVC, palmoplantar keratosis, and woolly hair

## TAKOTSUBO CARDIOMYOPATHY

Takotsubo cardiomyopathy is a type of non-ischaemic cardiomyopathy associated with a transient, apical ballooning of the myocardium. It may be triggered by stress.

Pathophysiology
- Takotsubo is a Japanese word that describes an octopus trap
- the apical ballooning appearance occurs due to severe hypokinesis of the mid and apical segments with preservation of activity of the basal segments. In simple terms, the bottom of the heart (the apex) does not contract and therefore appears to balloon out. However, the area closer to the top (the base) continues to contract (creating the neck of the octopus trap)

Features
- chest pain
- features of heart failure
- ECG: ST-elevation
- normal coronary angiogram

Treatment is supportive.

Prognosis
- the majority of patients improve with supportive treatment

# ATRIAL FIBRILLATION: A VERY BASIC INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is very common, being present in around 5% of patients over aged 70-75 years and 10% of patients aged 80-85 years. Whilst uncontrolled atrial fibrillation can result in symptomatic palpitations and inefficient cardiac function probably the most important aspect of managing patients with AF is reducing the increased risk of stroke which is present in these patients.

## ATRIAL FIBRILLATION: CLASSIFICATION

An attempt was made in the joint American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) 2012 guidelines to simplify and clarify the classification of atrial fibrillation (AF).

It is recommended that AF be classified into 3 patterns:

- first detected episode (irrespective of whether it is symptomatic or self-terminating)
- recurrent episodes, when a patient has 2 or more episodes of AF. If episodes of AF terminate spontaneously then the term paroxysmal AF is used. Such episodes last less than 7 days (typically < 24 hours). If the arrhythmia is not self-terminating then the term persistent AF is used. Such episodes usually last greater than 7 days
- in permanent AF there is continuous atrial fibrillation which cannot be cardioverted or if attempts to do so are deemed inappropriate. Treatment goals are therefore rate control and anticoagulation if appropriate

## Symptoms and signs

Symptoms

- palpitations
- dyspnoea
- chest pain

Signs

an irregularly irregular pulse

## Investigations

An ECG is essential to make the diagnosis as other conditions can give an irregular pulse, such as ventricular ectopics or sinus arrhythmia.

## Management

There are two key parts of managing patients with AF:

1. Rate/rhythm control
2. Reducing stroke risk

## Rate vs. rhythm control

There are two main strategies employed in dealing with the arrhythmia element of atrial fibrillation:

- **rate control:** accept that the pulse will be irregular, but slow the rate down to avoid negative effects on cardiac function
- **rhythm control:** try to get the patient back into, and maintain, normal sinus rhythm. This is termed cardioversion. Drugs (pharmacological cardioversion) and synchronised DC electrical shocks (electrical cardioversion) may be used for this purpose

For many years the predominant approach was to try and maintain a patient in sinus rhythm. This approach changed in the early 2000's and now the majority of patients are managed with a rate control strategy. NICE advocate using a rate control strategy except in a number of specific situations such as coexistent heart failure, first onset AF or where there is an obvious reversible cause.

## Rate control

A **beta-blocker** or a **rate-limiting calcium channel blocker** (e.g. diltiazem) is used first-line to control the rate in AF.

If one drug does not control the rate adequately NICE recommend combination therapy with any 2 of the following:

- a betablocker
- diltiazem
- digoxin

## Rhythm control

As mentioned above there are a subgroup of patients for whom a rhythm control strategy should be tried first. Other patients may have had a rate control strategy initially but switch to rhythm control if symptoms/heart rate fails to settle.

When considering cardioversion it is very important to remember that the moment a patient switches from AF to sinus rhythm presents the highest risk for embolism leading to stroke. Imagine the thrombus formed in the fibrillating atrium suddenly being pushed out when sinus rhythm is restored. For this reason patients must either have had a short duration of symptoms (less than 48 hours) or be anticoagulated for a period of time prior to attempting cardioversion.

### Reducing stroke risk

Some patients with AF are at a very low risk of stroke whilst others are at a very significant risk. Clinicians use risk stratifying tools such as the CHA2DS2-VASc score to determine the most appropriate anticoagulation strategy.

| | Risk factor | Points |
|---|---|---|
| **C** | Congestive heart failure | 1 |
| **H** | Hypertension (or treated hypertension) | 1 |
| **A$_2$** | Age >= 75 years | 2 |
| | Age 65-74 years | 1 |
| **D** | Diabetes | 1 |
| **S$_2$** | Prior Stroke or TIA | 2 |
| **V** | Vascular disease (including ischaemic heart disease and peripheral arterial disease) | 1 |
| **S** | Sex (female) | 1 |

The table below shows a suggested anticoagulation strategy based on the score:

| Score | Anticoagulation |
|---|---|
| 0 | No treatment |
| 1 | Males: Consider anticoagulation<br>Females: No treatment (this is because their score of 1 is only reached due to their gender) |
| 2 or more | Offer anticoagulation |

NICE recommend that we offer patients a choice of anticoagulation, including warfarin and the novel oral anticoagulants (NOACs).

## ATRIAL FIBRILLATION: ANTICOAGULATION

NICE updated their guidelines on the management of atrial fibrillation (AF) in 2014. They suggest using the CHA2DS2-VASc score to determine the most appropriate anticoagulation strategy. This scoring system superceded the CHADS2 score.

NICE recommend that we offer patients a choice of anticoagulation, including warfarin and the novel oral anticoagulants (NOACs). There are complicated rules surrounding which NOAC is licensed for which risk factor - these can be found in the NICE guidelines. Aspirin is no longer recommended for reducing stroke risk in patients with AF

Doctors have always thought carefully about the risk/benefit profile of starting someone on warfarin. A history of falls, old age, alcohol excess and a history of previous bleeding are common things that make us consider whether warfarinisation is in the best interests of the patient. NICE now recommend we formalise this risk assessment using the HASBLED scoring system.

| | **Risk factor** | **Points** |
|---|---|---|
| **H** | Hypertension, uncontrolled, systolic BP > 160 mmHg | 1 |
| **A** | Abnormal renal function (dialysis or creatinine > 200)<br>Or<br>Abnormal liver function (cirrhosis, bilirubin > 2 times normal, ALT/AST/ALP > 3 times normal | 1 for any renal abnormalities<br>1 for any liver abnormalities |
| **S** | Stroke, history of | 1 |
| **B** | Bleeding, history of bleeding or tendency to bleed | 1 |
| **L** | Labile INRs (unstable/high INRs, time in therapeutic range < 60%) | 1 |
| **E** | Elderly (> 65 years) | 1 |
| **D** | Drugs Predisposing to Bleeding (Antiplatelet agents, NSAIDs)<br>Or<br>Alcohol Use (>8 drinks/week) | 1 for drugs<br>1 for alcohol |

There are no formal rules on how we act on the HAS-BLED score although a score of >= 3 indicates a 'high risk' of bleeding, defined as intracranial haemorrhage, hospitalisation, haemoglobin decrease >2 g/L, and/or transfusion.

## ATRIAL FIBRILLATION: CARDIOVERSION

There are two scenarios where cardioversion may be used in atrial fibrillation:

- electrical cardioversion as an emergency if the patient is haemodynamically unstable

- electrical or pharmacological cardioversion as an elective procedure where a rhythm control strategy is preferred.

The notes below refer to cardioversion being used in the elective scenario for rhythm control. The wording of the 2014 NICE guidelines is as follows:

*offer rate or rhythm control if the onset of the arrhythmia is less than 48 hours, and start rate control if it is more than 48 hours or is uncertain*

**Onset < 48 hours**
If the atrial fibrillation (AF) is definitely of less than 48 hours onset patients should be heparinised. Patients who have risk factors for ischaemic stroke should be put on lifelong oral anticoagulation. Otherwise, patients may be cardioverted using either:

- electrical - 'DC cardioversion'
- pharmacology - amiodarone if structural heart disease, flecainide or amiodarone in those without structural heart disease

Following electrical cardioversion if AF is confirmed as being less than 48 hours duration then further anticoagulation is unnecessary

**Onset > 48 hours**
If the patient has been in AF for more than 48 hours then anticoagulation should be given for at least 3 weeks prior to cardioversion. An alternative strategy is to perform a transoesophageal echo (TOE) to exclude a left atrial appendage (LAA) thrombus. If excluded patients may be heparinised and cardioverted immediately.

NICE recommend electrical cardioversion in this scenario, rather than pharmacological.

If there is a high risk of cardioversion failure (e.g. Previous failure or AF recurrence) then it is recommend to have at least 4 weeks amiodarone or sotalol prior to electrical cardioversion

Following electrical cardioversion patients should be anticoagulated for at least 4 weeks. After this time decisions about anticoagulation should be taken on an individual basis depending on the risk of recurrence

# ATRIAL FIBRILLATION: PHARMACOLOGICAL CARDIOVERSION

NICE published guidelines on the management of atrial fibrillation (AF) in 2014. The following is also based on the joint American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) 2016 guidelines

Agents with proven efficacy in the pharmacological cardioversion of atrial fibrillation
- amiodarone
- flecainide (if no structural heart disease)
- others (less commonly used in UK): quinidine, dofetilide, ibutilide, propafenone

Less effective agents
- beta-blockers (including sotalol)
- calcium channel blockers
- digoxin
- disopyramide
- procainamide

# ATRIAL FIBRILLATION: POST-STROKE

NICE issued guidelines on atrial fibrillation (AF) in 2006. They included advice on the management of patients with AF who develop a stroke or transient-ischaemic attack (TIA).

Recommendations include:
- following a stroke or TIA, warfarin or a direct thrombin or factor Xa inhibitor should be given as the anticoagulant of choice. Antiplatelets should only be given if needed for the treatment of other comorbidities
- in acute stroke patients, in the absence of haemorrhage, anticoagulation therapy should be commenced after 2 weeks. If imaging shows a very large cerebral infarction then the initiation of anticoagulation should be delayed

# ATRIAL FIBRILLATION: RATE CONTROL AND MAINTENANCE OF SINUS RHYTHM

The Royal College of Physicians and NICE published guidelines on the management of atrial fibrillation (AF) in 2006. The following is also based on the joint American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) 2012 guidelines

## Medication

Agents used to control rate in patients with atrial fibrillation

- beta-blockers
- calcium channel blockers
- digoxin (not considered first-line anymore as they are less effective at controlling the heart rate during exercise. However, they are the preferred choice if the patient has coexistent heart failure)

Agents used to maintain sinus rhythm in patients with a history of atrial fibrillation

- sotalol
- amiodarone
- flecainide
- others (less commonly used in UK): disopyramide, dofetilide, procainamide, propafenone, quinidine

The table below indicates some of the factors which may be considered when considering either a rate control or rhythm control strategy

| Factors favouring rate control | Factors favouring rhythm control |
|---|---|
| Older than 65 years<br>History of ischaemic heart disease | Younger than 65 years<br>Symptomatic<br>First presentation<br>Lone AF or AF secondary to a corrected precipitant (e.g. Alcohol)<br>Congestive heart failure |

## Catheter ablation

NICE recommends the use of catheter ablation for those with AF who have not responded to or wish to avoid, antiarrhythmic medication.

Technical aspects

- the aim is to ablate the faulty electrical pathways that are resulting in atrial fibrillation. This is typically due to aberrant electrical activity between the pulmonary veins and left atrium
- the procedure is performed percutaneously, typically via the groin
- both radiofrequency (uses heat generated from medium frequency alternating current) and cryotherapy can be used to ablate the tissue

Anticoagulation

- should be used 4 weeks before and during the procedure
- it should be remember that catheter ablation controls the rhythm but does not reduce the stroke risk, even if patients remain in sinus rhythm. Therefore, patients still require anticoagulation as per there CHA2DS2-VASc score
- if score = 0: 2 months anticoagulation recommended
- if score > 1: longterm anticoagulation recommended

Outcome

- notable complications include
  - cardiac tamponade
  - stroke
  - pulmonary valve stenosis
- success rate
  - around 50% of patients experience an early recurrence (within 3 months) of AF that often resolves spontaneously
  - longer term, after 3 years, around 55% of patients who've had a single procedure remain in sinus rhythm. Of patient who've undergone multiple procedures around 80% are in sinus rhythm

## COMBINATION ANTIPLATELET AND ANTICOAGULANT THERAPY

With the increase in comorbidity, it is now common to find that a patient has an indication for both an antiplatelet (e.g. established cardiovascular disease) and an anticoagulant (e.g. atrial fibrillation, venous thromboembolism or valvular heart disease). However, combination therapy increases the risk of bleeding and may not be needed in all cases. How should this be managed?

Whilst there are not guidelines to cover every scenario a recent review in the BMJ offered an expert opinion outlining the approach in common scenarios.

Secondary prevention of stable cardiovascular disease with an indication for an anticoagulant

- normally in this situation, all patients are recommended to be prescribed an antiplatelet
- if an indication for anticoagulant exists (for example atrial fibrillation) it is indicated that anticoagulant monotherapy is given without the addition of antiplatelets

Post-acute coronary syndrome/percutaneous coronary intervention

- in these patients, there is a much stronger indication for antiplatelet therapy
- generally patients are given triple therapy (2 antiplatelets + 1 anticoagulant) for 4 weeks-6 months after the event and dual therapy (1 antiplatelet + 1 anticoagulant) to complete 12 months
- there is variation from patient to patient however given that the stroke risk in atrial fibrillation varies according to risk factors.

Venous thromboembolism (VTE)

- if a patient on antiplatelets develops a VTE they are likely to be prescribed anticoagulants for 3-6 months
- a HAS-BLED score should be calculated. Those with a low risk of bleeding may continue antiplatelets. In patients with an intermediate or high risk of bleeding consideration should be given to stopping the antiplatelets

For more information please see BMJ 2017;358:j3782

## ANTIPLATELETS: SUMMARY OF LATEST GUIDANCE

The table below summarises the most recent guidelines regarding antiplatelets:

| Diagnosis | 1st line | 2nd line |
|---|---|---|
| Acute coronary syndrome (medically treated) | Aspirin (lifelong) & ticagrelor (12 months) | If aspirin contraindicated, clopidogrel (lifelong) |
| Percutaneous coronary intervention | Aspirin (lifelong) & prasurgrel or ticagrelor (12 months) | If aspirin contraindicated, clopidogrel (lifelong) |

| Diagnosis | 1st line | 2nd line |
|---|---|---|
| TIA | Clopidogrel (lifelong) | Aspirin (lifelong) & dipyridamole (lifelong) |
| Ischaemic stroke | Clopidogrel (lifelong) | Aspirin (lifelong) & dipyridamole (lifelong) |
| Peripheral arterial disease | Clopidogrel (lifelong) | Asprin (lifelong) |

# WARFARIN

Warfarin is an oral anticoagulant which inhibits epoxide reductase preventing the reduction of vitamin K to its active hydroquinone form, which in turn acts as a cofactor in the carboxylation of clotting factor II, VII, IX and X (mnemonic = 1972) and protein C.

Indications

- venous thromboembolism: target INR = 2.5, if recurrent 3.5
- atrial fibrillation, target INR = 2.5
- mechanical heart valves, target INR depends on the valve type and location. Mitral valves generally require a higher INR than aortic valves.

Patients on warfarin are monitored using the INR (international normalised ration), the ratio of the prothrombin time for the patient over the normal prothrombin time. Warfarin has a long half-life and achieving a stable INR may take several days. There a variety of loading regimes and computer software is now often used to alter the dose.

Factors that may potentiate warfarin

- liver disease
- P450 enzyme inhibitors, e.g.: amiodarone, ciprofloxacin
- cranberry juice
- drugs which displace warfarin from plasma albumin, e.g. NSAIDs
- inhibit platelet function: NSAIDs

Side-effects

- haemorrhage
- teratogenic, although can be used in breastfeeding mothers
- skin necrosis: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin,

normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis
- purple toes

## WARFARIN: MANAGEMENT OF HIGH INR

The following is based on the BNF guidelines, which in turn take into account the British Committee for Standards in Haematology (BCSH) guidelines. A 2005 update of the BCSH guidelines emphasised the preference of prothrombin complex concentrate over FFP in major bleeding.

| Situation | Management |
|---|---|
| **Major bleeding** | Stop warfarin<br>Give intravenous vitamin K 5mg<br>Prothrombin complex concentrate - if not available then FFP* |
| **INR > 8.0<br>Minor bleeding** | Stop warfarin<br>Give intravenous vitamin K 1-3mg<br>Repeat dose of vitamin K if INR still too high after 24 hours<br>Restart warfarin when INR < 5.0 |
| **INR > 8.0<br>No bleeding** | Stop warfarin<br>Give vitamin K 1-5mg by mouth, using the intravenous preparation orally<br>Repeat dose of vitamin K if INR still too high after 24 hours<br>Restart when INR < 5.0 |
| **INR 5.0-8.0<br>Minor bleeding** | Stop warfarin<br>Give intravenous vitamin K 1-3mg<br>Restart when INR < 5.0 |
| **INR 5.0-8.0<br>No bleeding** | Withhold 1 or 2 doses of warfarin<br>Reduce subsequent maintenance dose |

*as FFP can take time to defrost prothrombin complex concentrate should be considered in cases of intracranial haemorrhage

## CLOPIDOGREL

Clopidogrel is an antiplatelet agent used in the management of cardiovascular disease. It was previously used when aspirin was not tolerated or contraindicated but there are now a number of conditions for which clopidogrel is used in addition to aspirin, for example in patients with an acute coronary syndrome. Following the 2010 NICE technology appraisal clopidogrel is also now first-line in patients following an ischaemic stroke and in patients with peripheral arterial disease.

Clopidogrel belongs to a class of drugs known as thienopyridines which have a similar mechanism of action. Other examples include:
- prasugrel
- ticagrelor
- ticlopidine

Mechanism
- antagonist of the P2Y12 adenosine diphosphate (ADP) receptor, inhibiting the activation of platelets

Interactions
- concurrent use of proton pump inhibitors (PPIs) may make clopidogrel less effective (MHRA July 2009)
- this advice was updated by the MHRA in April 2010, evidence seems inconsistent but omeprazole and esomeprazole still cause for concern. Other PPIs such as lansoprazole should be OK - please see the link for more details

## DIPYRIDAMOLE

Dipyridamole is an antiplatelet mainly used in combination with aspirin after an ischaemic stroke or transient ischaemic attack.

Mechanism of action
- inhibits phosphodiesterase, elevating platelet cAMP levels which in turn reduce intracellular calcium levels

- other actions include reducing cellular uptake of adenosine and inhibition of thromboxane synthase

## DABIGATRAN

Dabigatran is an oral anticoagulant that works by being a direct thrombin inhibitor. It is one of the drugs developed over the past 10-15 years as an alternative to warfarin, with the advantage that it does not require regular monitoring.

**What is dabigatran used for?**
Dabigatran is currently used for two main indications.

Firstly it is an option in the prophylaxis of venous thromboembolism following hip or knee replacement surgery.

Secondly, it is also licensed in the UK for prevention of stroke in patients with non-valvular atrial fibrillation who have one or more of the following risk factors present:
- previous stroke, transient ischaemic attack or systemic embolism
- left ventricular ejection fraction below 40%
- symptomatic heart failure of New York Heart Association (NYHA) class 2 or above
- age 75 years or older
- age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension

**What are the known side-effects of dabigatran?**
Unsurprisingly haemorrhage is the major adverse effect.

Doses should be reduced in chronic kidney disease and dabigatran should not be prescribed if the creatinine clearance is < 30 ml/min.

**Drug Safety Update 2013**
The RE-ALIGN study showed significantly higher bleeding and thrombotic events in patients with recent mechanical heart valve replacement using dabigatran compared with warfarin.

Previously there had been no guidance to support the use of dabigatran in patients with prosthetic heart valves but the advice has now changed to dabigatran being contraindicated in such patients.

## ATRIAL FLUTTER

Atrial flutter is a form of supraventricular tachycardia characterised by a succession of rapid atrial depolarisation waves.

ECG findings
- 'sawtooth' appearance
- as the underlying atrial rate is often around 300/min the ventricular or heart rate is dependent on the degree of AV block. For example if there is 2:1 block the ventricular rate will be 150/min
- flutter waves may be visible following carotid sinus massage or adenosine

Management
- is similar to that of atrial fibrillation although medication may be less effective
- atrial flutter is more sensitive to cardioversion however so lower energy levels may be used
- radiofrequency ablation of the tricuspid valve isthmus is curative for most patients

## SUPRAVENTRICULAR TACHYCARDIA

Whilst strictly speaking the term supraventricular tachycardia (SVT) refers to any tachycardia that is not ventricular in origin the term is generally used in the context of paroxysmal SVT. Episodes are characterised by the sudden onset of a narrow complex tachycardia, typically an atrioventricular nodal re-entry tachycardia (AVNRT). Other causes include atrioventricular re-entry tachycardias (AVRT) and junctional tachycardias.

Acute management
- vagal manoeuvres: e.g. Valsalva manoeuvre, carotid sinus massage
- intravenous adenosine 6mg → 12mg → 12mg: contraindicated in asthmatics - verapamil is a preferable option
- electrical cardioversion

Prevention of episodes
- beta-blockers
- radio-frequency ablation

## VALSALVA MANOEUVRE

The Valsalva manoeuvre describes a forced expiration against a closed glottis. This leads to increased intrathoracic pressure which in turn has a number of effects on the cardiovascular system.

Uses
- to terminate an episode of supraventricular tachycardia
- normalizing middle-ear pressures

Stages of the Valsalva manoeuvre
1. Increased intrathoracic pressure
2. Resultant increase in venous and right atrial pressure reduces venous return
3. The reduced preload leads to a fall in the cardiac output (Frank-Starling mechanism)
4. When the pressure is released there is a further slight fall in cardiac output due to increased aortic volume
5. Return of normal cardiac output

## ADENOSINE

Adenosine is most commonly used to terminate supraventricular tachycardias. The effects of adenosine are enhanced by dipyridamole (antiplatelet agent) and blocked by theophyllines. It should be avoided in asthmatics due to possible bronchospasm.

Mechanism of action
- causes transient heart block in the AV node
- agonist of the A1 receptor in the atrioventricular node, which inhibits adenylyl cyclase thus reducing cAMP and causing hyperpolarization by increasing outward potassium flux
- adenosine has a very short half-life of about 8-10 seconds

Adenosine should ideally be infused via a large-calibre cannula due to it's short half-life,

Adverse effects
- chest pain
- bronchospasm
- transient flushing
- can enhance conduction down accessory pathways, resulting in increased ventricular rate (e.g. WPW syndrome)

## ADENOSINE DIPHOSPHATE (ADP) RECEPTOR INHIBITORS

Examples include:
- Clopidogrel
- Prasugrel
- Ticagrelor
- Ticlopidine

Mechanism of ADP receptor inhibitors
- Adenosine diphosphate (ADP) is one of the main platelet activation factors, mediated by G-coupled receptors P2Y1 and P2Y12.
- The main target of ADP receptor inhibition is the P2Y12 receptor, as it is the one which leads to sustained platelet aggregation and stabilisation of the platelet plaque.

Evidence
- As aspirin and ADP inhibitors work by blocking different platelet aggregation pathways, their potential synergy has been studied by multiple clinical trials, particularly in high-risk patients presenting with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI).
- Clopidogrel used to be the most commonly used ADP inhibitor, however, due to its interindividual variability in antiplatelet effects, newer agents such as prasugrel and ticagrelor have been developed.

- Multiple trials since have shown a marked reduction in short- and long-term ischaemic events when using prasugrel and aspirin, compared to clopidogrel and aspirin in moderate- to high-risk ACS patients.1
- Current NICE guidelines for ACS, therefore, recommend starting dual antiplatelet treatment (DAPT) with Aspirin (75mg daily) and Ticagrelor (90mg twice daily) for 12 months, as a secondary prevention strategy.
- NICE guidelines for people with ACS undergoing PCI recommend aspirin (75-100mg daily) in combination with either prasugrel (10mg daily), ticagrelor (90mg twice daily), or clopidogrel (75mg daily, if prasugrel or ticagrelor are not suitable) for 12 months, with aspirin alone thereafter.2

Notable adverse effects

- ticagrelor may cause dyspnoea
    - due to the impaired clearance of adenosine

Interactions and contraindications

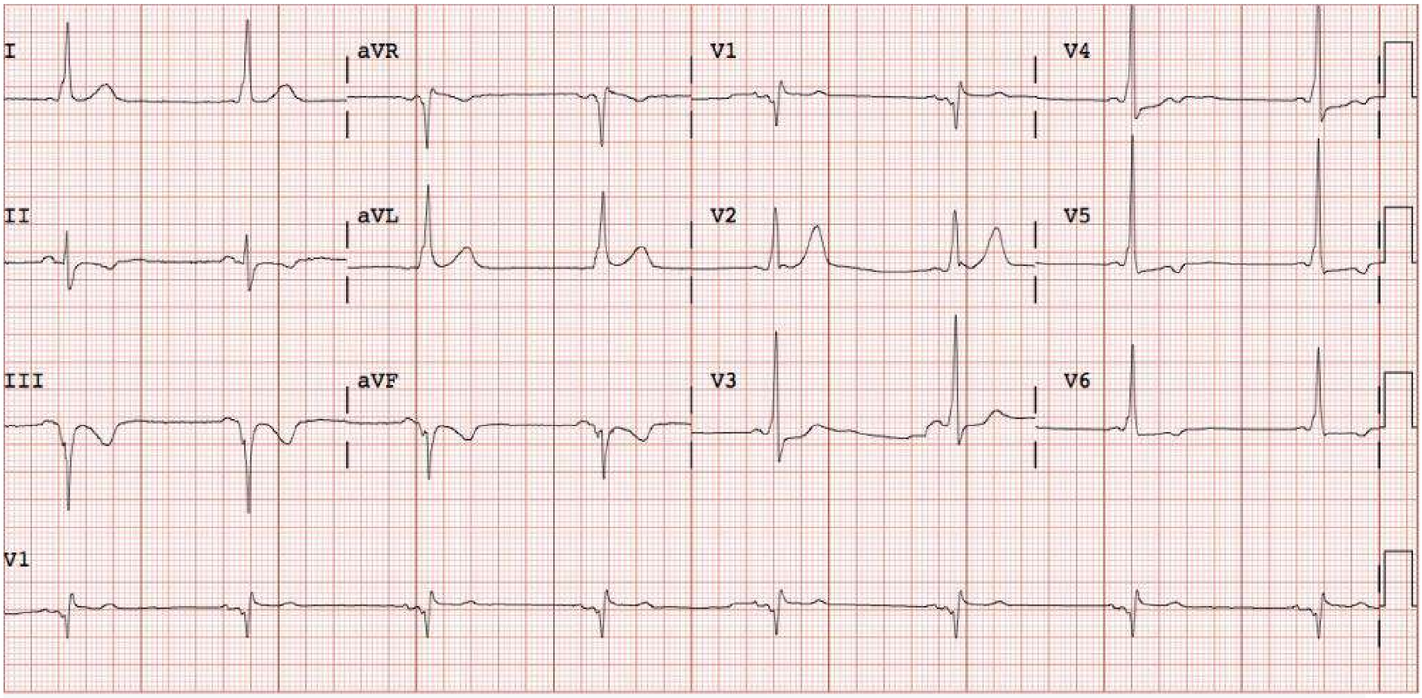
- A drug interaction exists between clopidogrel and proton pump inhibitors, particularly omeprazole and esomeprazole, leading to reducing antiplatelet effects.
- Patients with prior stroke or transient ischaemic attack, high risk of bleeding, and prasugrel hypersensitivity are absolute contraindications to prasugrel use.
- Ticagrelor is contraindicated in patients with a high risk of bleeding, those with a history of intracranial haemorrhage, and those with severe hepatic dysfunction. It is also to be used with caution in those with acute asthma or COPD, as ticagrelor-treated patients experience higher rates of dyspnoea.1

## **WOLFF-PARKINSON WHITE**

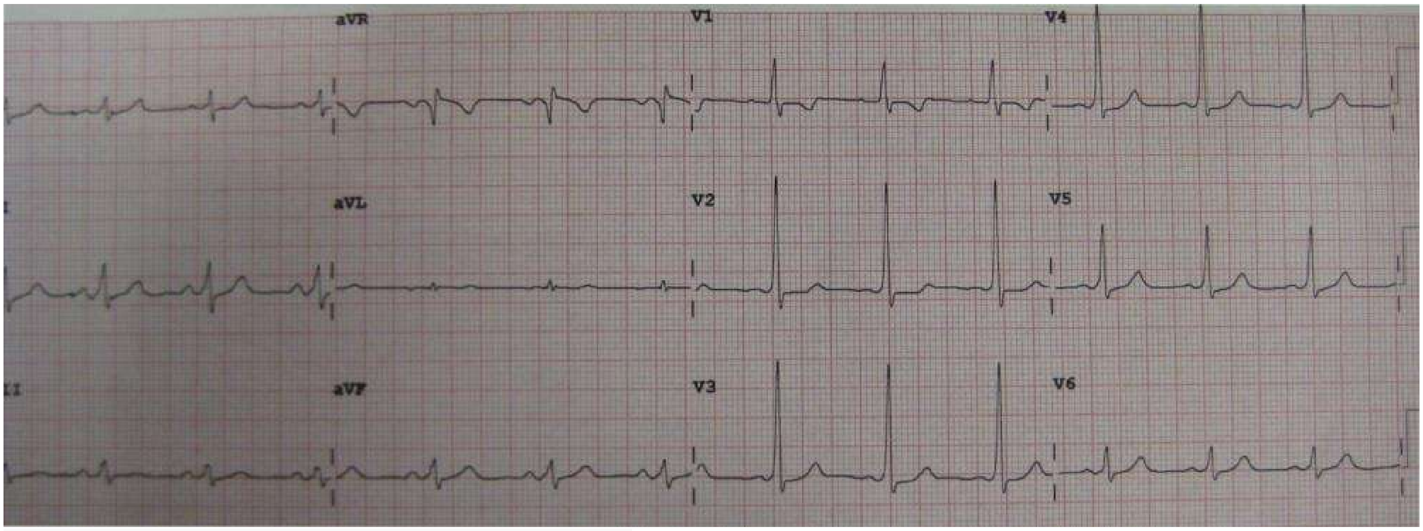
Wolff-Parkinson White (WPW) syndrome is caused by a congenital accessory conducting pathway between the atria and ventricles leading to a atrioventricular re-entry tachycardia (AVRT). As the accessory pathway does not slow conduction AF can degenerate rapidly to VF

Possible ECG features include:

- short PR interval
- wide QRS complexes with a slurred upstroke - 'delta wave'
- left axis deviation if right-sided accessory pathway*
- right axis deviation if left-sided accessory pathway*


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1

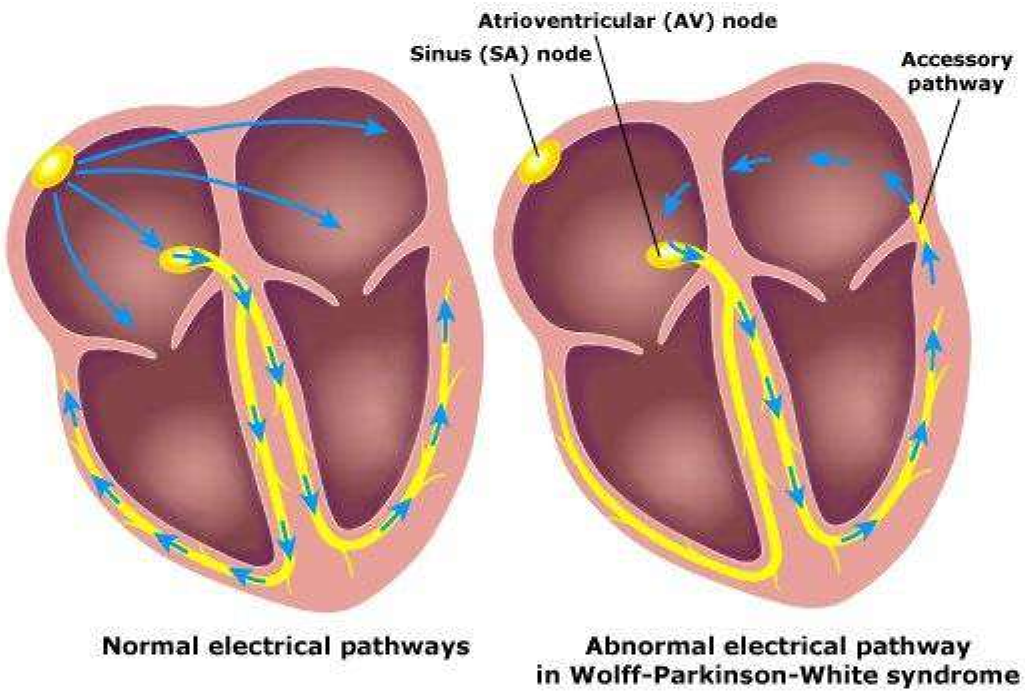
ECG showing short PR interval associated with a slurred upstroke (delta wave). Note the non-specific ST-T changes which are common in WPW and may be mistaken for ischaemia. The left axis deviation means that this is type B WPW, implying a right-sided pathway


aVR
V1
V4
aVL
V2
V5
II
aVF
V3
V6

Further example showing a characteristic delta wave

Differentiating between type A and type B**

- type A (left-sided pathway): dominant R wave in V1
- type B (right-sided pathway): no dominant R wave in V1


Atrioventricular (AV) node
Sinus (SA) node
Accessory pathway
Normal electrical pathways
Abnormal electrical pathway in Wolff-Parkinson-White syndrome

Associations of WPW
- HOCM
- mitral valve prolapse
- Ebstein's anomaly
- thyrotoxicosis
- secundum ASD

Management
- definitive treatment: radiofrequency ablation of the accessory pathway
- medical therapy: sotalol***, amiodarone, flecainide

*in the majority of cases, or in a question without qualification, Wolff-Parkinson-White syndrome is associated with left axis deviation

**there is a rare type C WPW, WPW in which the delta waves are upright in leads V1-V4 but negative in leads V5-V6

***sotalol should be avoided if there is coexistent atrial fibrillation as prolonging the refractory period at the AV node may increase the rate of transmission through the accessory pathway, increasing the ventricular rate and potentially deteriorating into ventricular fibrillation

# MULTIFOCAL ATRIAL TACHYCARDIA

Multifocal atrial tachycardia (MAT) may be defined as a irregular cardiac rhythm caused by at least three different sites in the atria, which may be demonstrated by morphologically distinctive P waves. It is more common in elderly patients with chronic lung disease, for example COPD

Management
- correction of hypoxia and electrolyte disturbances
- rate-limiting calcium channel blockers are often used first-line
- cardioversion and digoxin are not useful in the management of MAT

# VENTRICULAR TACHYCARDIA

Ventricular tachycardia (VT) is broad-complex tachycardia originating from a ventricular ectopic focus. It has the potential to precipitate ventricular fibrillation and hence requires urgent treatment.

There are two main types of VT:
- monomorphic VT: most commonly caused by myocardial infarction
- polymorphic VT: A subtype of polymorphic VT is torsades de pointes which is precipitated by prolongation of the QT interval. The causes of a long QT interval are listed below

Causes of a prolonged QT interval

| **Congenital** | **Drugs** | **Other** |
|---|---|---|
| • Jervell-Lange-Nielsen syndrome (includes deafness and is due to an abnormal potassium channel)<br>• Romano-Ward syndrome (no deafness) |  amiodarone, sotalol, class 1a antiarrhythmic drugs<br> tricyclic antidepressants, fluoxetine<br> chloroquine<br> terfenadine<br> erythromycin |  electrolyte: hypocalcaemia, hypokalaemia, hypomagnesaemia<br> acute myocardial infarction<br> myocarditis<br> hypothermia<br> subarachnoid haemorrhage |

# VENTRICULAR TACHYCARDIA: MANAGEMENT

Whilst a broad complex tachycardia may result from a supraventricular rhythm with aberrant conduction, the European Resuscitation Council advise that in a peri-arrest situation it is assumed to be ventricular in origin

If the patient has adverse signs (systolic BP < 90 mmHg, chest pain, heart failure) then immediate cardioversion is indicated. In the absence of such signs antiarrhythmics may be used. If these fail, then electrical cardioversion may be needed with synchronised DC shocks

Drug therapy
- amiodarone: ideally administered through a central line
- lidocaine: use with caution in severe left ventricular impairment
- procainamide

Verapamil should NOT be used in VT

If drug therapy fails
- electrophysiological study (EPS)
- implant able cardioverter-defibrillator (ICD) - this is particularly indicated in patients with significantly impaired LV function

# AMIODARONE

Amiodarone is a class III antiarrhythmic agent used in the treatment of atrial, nodal and ventricular tachycardias. The main mechanism of action is by blocking potassium channels which inhibits repolarisation and hence prolongs the action potential. Amiodarone also has other actions such as blocking sodium channels (a class I effect)

The use of amiodarone is limited by a number of factors
- very long half-life (20-100 days). For this reason, loading doses are frequently used
- should ideally be given into central veins (causes thrombophlebitis)
- has proarrhythmic effects due to lengthening of the QT interval
- interacts with drugs commonly used concurrently (p450 inhibitor) e.g. Decreases metabolism of warfarin

- numerous long-term adverse effects (see below)

Monitoring of patients taking amiodarone
- TFT, LFT, U&E, CXR prior to treatment
- TFT, LFT every 6 months

Adverse effects of amiodarone use
- thyroid dysfunction: both hypothyroidism and hyper-thyroidism
- corneal deposits
- pulmonary fibrosis/pneumonitis
- liver fibrosis/hepatitis
- peripheral neuropathy, myopathy
- photosensitivity
- 'slate-grey' appearance
- thrombophlebitis and injection site reactions
- bradycardia
- lengths QT interval

# CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a form of inherited cardiac disease associated with sudden cardiac death. It is inherited in an autosomal dominant fashion and has a prevalence of around 1:10,000.

Pathophysiology
- the most common cause is a defect in the ryanodine receptor (RYR2) which is found in the myocardial sarcoplasmic reticulum

Features
- exercise or emotion induced polymorphic ventricular tachycardia resulting in syncope
- sudden cardiac death
- symptoms generally develop before the age of 20 years

Management

- beta-blockers
- implantable cardioverter-defibrillato

# CARDIAC TAMPONADE

Cardiac tamponade is characterized by the accumulation of pericardial fluid under pressure.

Classical features - Beck's triad:
- hypotension
- raised JVP
- muffled heart sounds

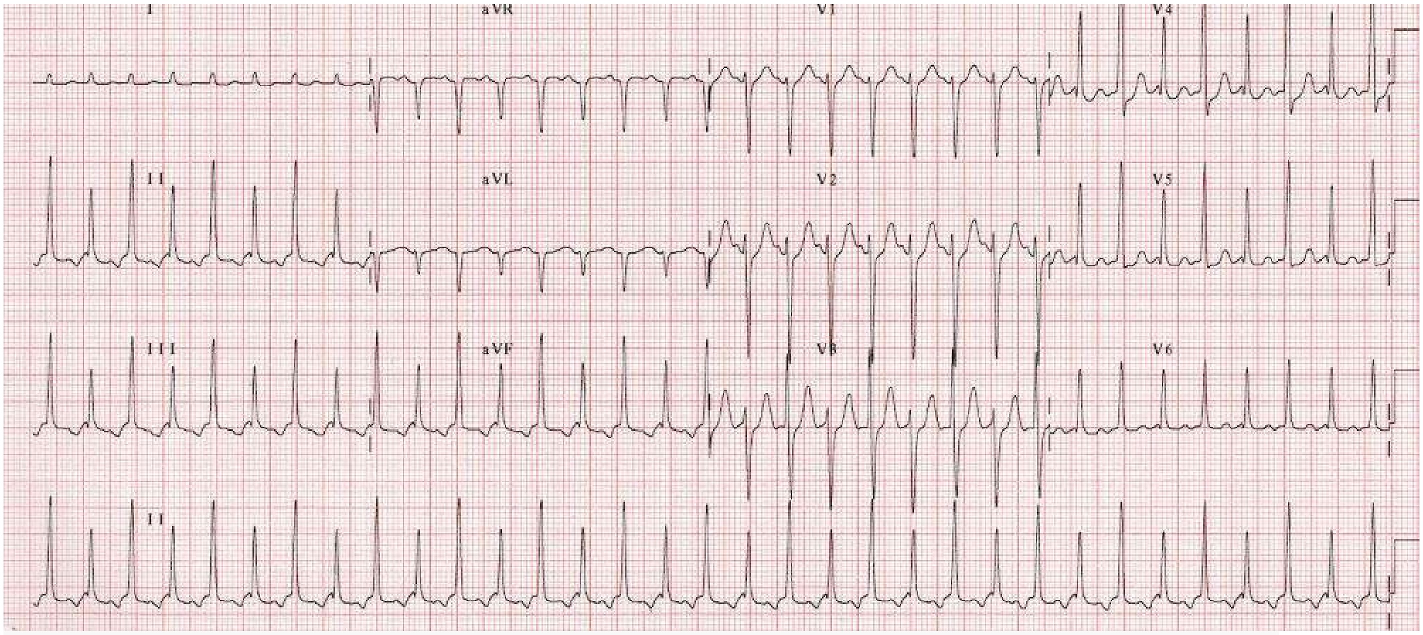
Other features:
- dyspnoea
- tachycardia
- an absent Y descent on the JVP - this is due to the limited right ventricular filling
- pulsus paradoxus - an abnormally large drop in BP during inspiration
- Kussmaul's sign - much debate about this
- ECG: electrical alternans

The key differences between constrictive pericarditis and cardiac tamponade are summarised in the table below:

| | **Cardiac tamponade** | **Constrictive pericarditis** |
|---|---|---|
| **JVP** | Absent Y descent | X + Y present |
| **Pulsus paradoxus** | Present | Absent |
| **Kussmaul's sign** | Rare | Present |
| **Characteristic features** | | Pericardial calcification on CXR |

A commonly used mnemonic to remember the absent Y descent in cardiac tamponade is TAMponade = TAMpaX

Management
- urgent pericardiocentesis


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

An ECG demonstrating electrical alternans. Note the alternation of QRS complex amplitude between beats.

# COARCTATION OF THE AORTA

Coarctation of the aorta describes a congenital narrowing of the descending aorta.

Overview
- more common in males (despite association with Turner's syndrome)

Features
- infancy: heart failure
- adult: hypertension
- radio-femoral delay
- mid systolic murmur, maximal over back
- apical click from the aortic valve
- notching of the inferior border of the ribs (due to collateral vessels) is not seen in young children

Associations
- Turner's syndrome
- bicuspid aortic valve
- berry aneurysms
- neurofibromatosis

# AORTIC DISSECTION

Aortic dissection is a rare but serious cause of chest pain.

Pathophysiology
- tear in the tunica intima of the wall of the aorta

Associations
- hypertension: the most important risk factor
- trauma
- bicuspid aortic valve
- collagens: Marfan's syndrome, Ehlers-Danlos syndrome
- Turner's and Noonan's syndrome
- pregnancy
- syphilis

Features:

- chest pain: typically severe, radiates through to the back and 'tearing' in nature
- aortic regurgitation
- hypertension
- other features may result from the involvement of specific arteries. For example coronary arteries → angina, spinal arteries → paraplegia, distal aorta → limb ischaemia
- the majority of patients have no or non-specific ECG changes. In a minority of patients, ST-segment elevation may be seen in the inferior leads

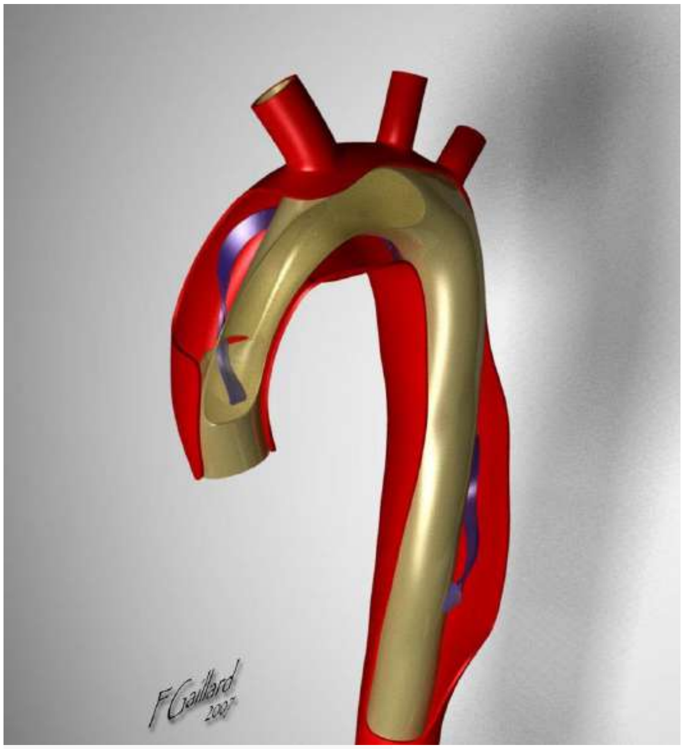
### Classification

Stanford classification

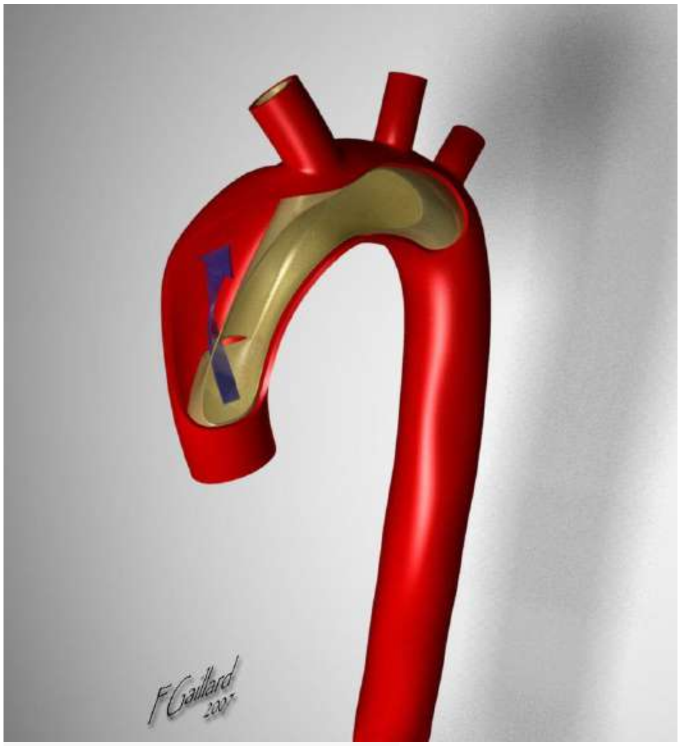
- type A - ascending aorta, 2/3 of cases
- type B - descending aorta, distal to left subclavian origin, 1/3 of cases

DeBakey classification

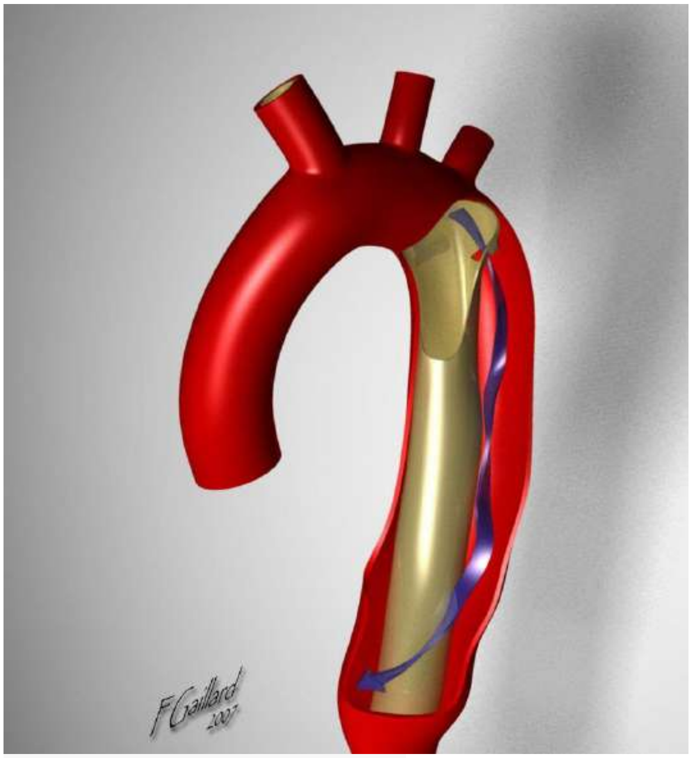
- type I - originates in ascending aorta, propagates to at least the aortic arch and possibly beyond it distally
- type II - originates in and is confined to the ascending aorta
- type III - originates in descending aorta, rarely extends proximally but will extend distally



Stanford type A / DeBakey type I



Stanford type A / DeBakey type II



Stanford type B / DeBakey type III

# AORTIC DISSECTION: MANAGEMENT

**Classification**
Stanford classification
type A - ascending aorta, 2/3 of cases
type B - descending aorta, distal to left subclavian origin, 1/3 of cases

DeBakey classification
type I - originates in ascending aorta, propagates to at least the aortic arch and possibly beyond it distally
type II - originates in and is confined to the ascending aorta
type III - originates in descending aorta, rarely extends proximally but will extend distally

**Management**
Type A

- surgical management, but blood pressure should be controlled to a target systolic of 100-120 mmHg whilst awaiting intervention

Type B*

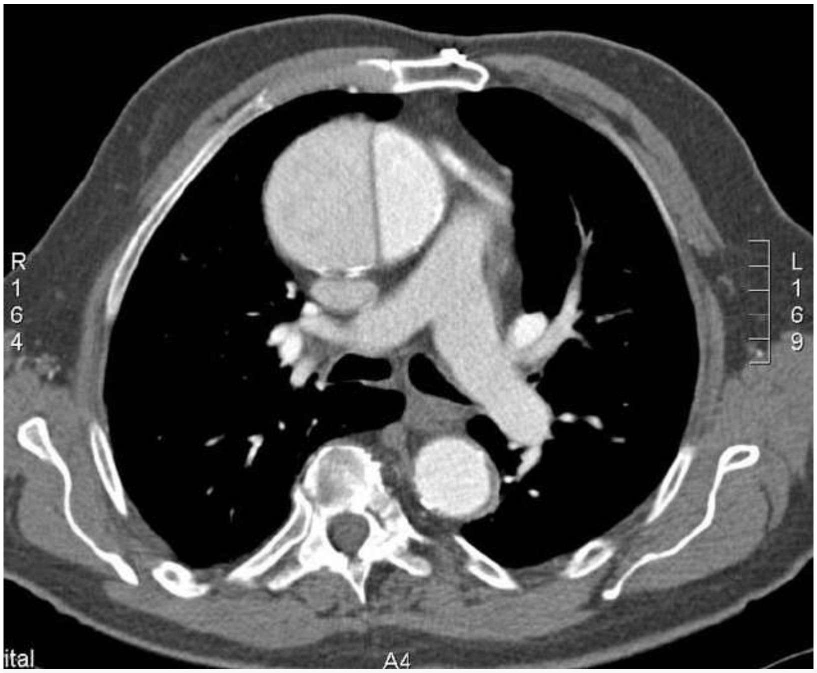
- conservative management
- bed rest
- reduce blood pressure IV labetalol to prevent progression

**Complications**
Complications of backward tear

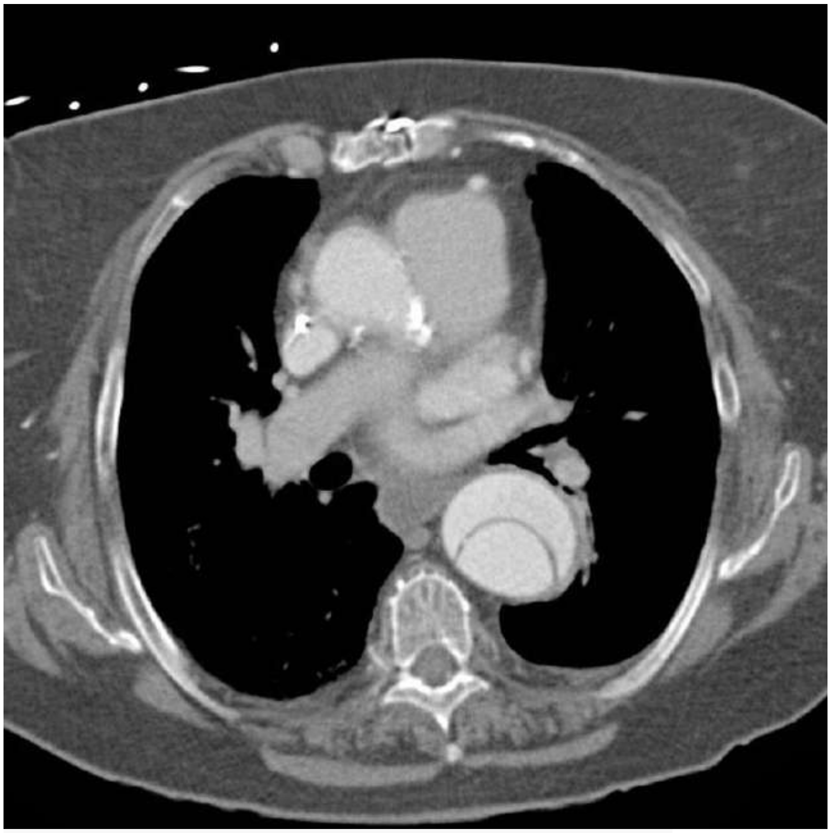
- aortic incompetence/regurgitation
- MI: inferior pattern often seen due to right coronary involvement

Complications of forward tear

- unequal arm pulses and BP
- stroke
- renal failure



An intraluminal tear has formed a 'flap' that can be clearly seen in the ascending aorta. This is a Stanford type A dissection



Stanford type B dissection, seen in the descending aorta

*endovascular repair of type B aortic dissection may have a role in the future

# ATRIOVENTRICULAR BLOCK

In atrioventricular (AV) block, or heart block, there is impaired electrical conduction between the atria and ventricles. There are three types:

First-degree heart block
- PR interval > 0.2 seconds
- asymptomatic first-degree heart block is relatively common and does not need treatment

Second-degree heart block
- type 1 (Mobitz I, Wenckebach): progressive prolongation of the PR interval until a dropped beat occurs
- type 2 (Mobitz II): PR interval is constant but the P wave is often not followed by a QRS complex

Third-degree (complete) heart block
- there is no association between the P waves and QRS complexes

# COMPLETE HEART BLOCK

Features
- syncope
- heart failure
- regular bradycardia (30-50 bpm)
- wide pulse pressure
- JVP: cannon waves in neck
- variable intensity of S1

**Types of heart block**

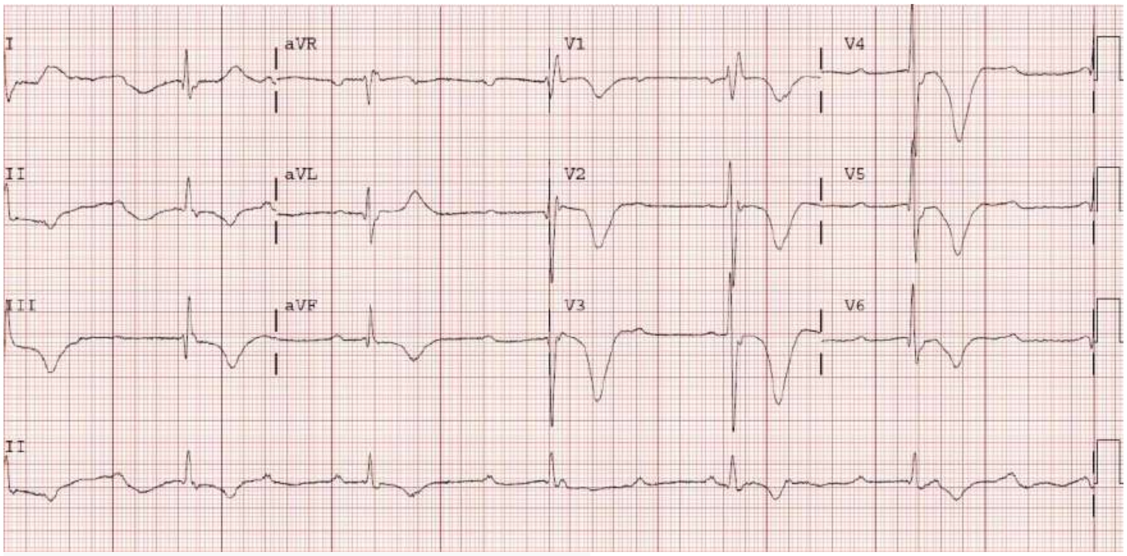
First degree heart block
- PR interval > 0.2 seconds

Second degree heart block
- type 1 (Mobitz I, Wenckebach): progressive prolongation of the PR interval until a dropped beat occurs

- type 2 (Mobitz II): PR interval is constant but the P wave is often not followed by a QRS complex

Third degree (complete) heart block

- there is no association between the P waves and QRS complexes


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

ECG showing third degree (complete) heart block

# CORONARY CIRCULATION

Arterial supply of the heart

- left aortic sinus → left coronary artery (LCA)
- right aortic sinus → right coronary artery (RCA)
- LCA → LAD + circumflex
- RCA → posterior descending
- RCA supplies SA node in 60%, AV node in 90%

Venous drainage of the heart

- coronary sinus drains into the right atrium

The coronary arteries fill during diastole.

# ECG: AXIS DEVIATION

Causes of left axis deviation (LAD)

- left anterior hemiblock
- left bundle branch block
- inferior myocardial infarction
- Wolff-Parkinson-White syndrome* - right-sided accessory pathway
- hyperkalaemia
- congenital: ostium primum ASD, tricuspid atresia
- minor LAD in obese people

Causes of right axis deviation (RAD)

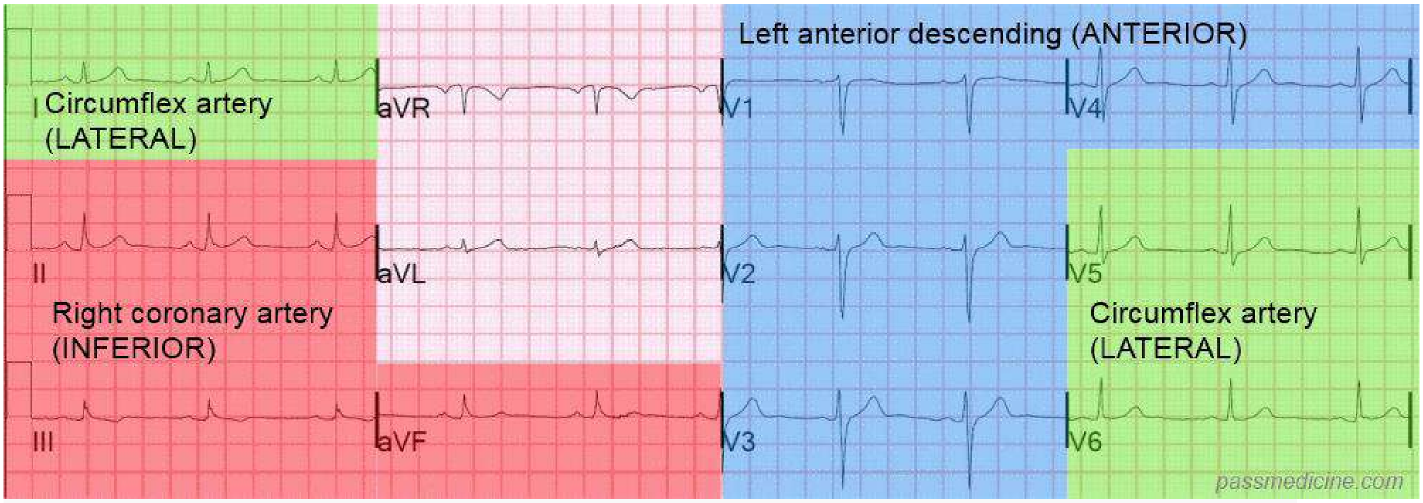
- right ventricular hypertrophy
- left posterior hemiblock
- lateral myocardial infarction
- chronic lung disease → cor pulmonale
- pulmonary embolism
- ostium secundum ASD
- Wolff-Parkinson-White syndrome* - left-sided accessory pathway
- normal in infant < 1 years old
- minor RAD in tall people

# ECG: CORONARY TERRITORIES

The table below shows the correlation between ECG changes and coronary territories:

| | ECG changes | Coronary artery |
|---|---|---|
| **Anteroseptal** | V1-V4 | Left anterior descending |
| **Inferior** | II, III, aVF | Right coronary |
| **Anterolateral** | V4-6, I, aVL | Left anterior descending or left circumflex |
| **Lateral** | I, aVL +/- V5-6 | Left circumflex |
| **Posterior** | Tall R waves V1-2 | Usually left circumflex, also right coronary |

It should be remembered that a new left bundle branch block (LBBB) may point towards a diagnosis of acute coronary syndrome.



Circumflex artery (LATERAL)
I
aVR
Left anterior descending (ANTERIOR)
V1
V4
II
aVL
V2
V5
Right coronary artery (INFERIOR)
Circumflex artery (LATERAL)
III
aVF
V3
V6
passmedicine.com

Diagram showing the correlation between ECG changes and coronary territories in acute coronary syndrome

# ECG: DIGOXIN

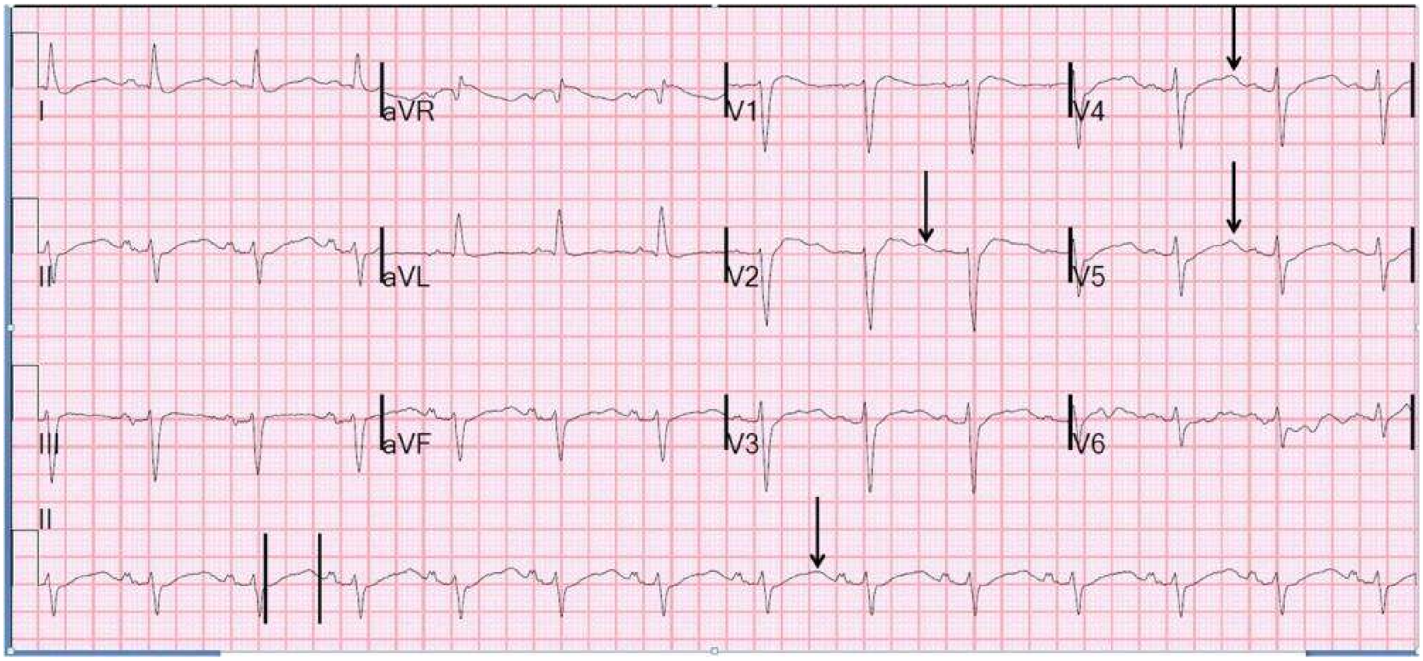
ECG features

- down-sloping ST depression ('reverse tick')
- flattened/inverted T waves
- short QT interval
- arrhythmias e.g. AV block, bradycardia

## ECG: HYPOKALAEMIA

ECG features of hypokalaemia
- U waves
- small or absent T waves (occasionally inversion)
- prolong PR interval
- ST depression
- long QT

The ECG below shows typical U waves. Note also the borderline PR interval.



One registered user suggests the following rhyme
- In Hypokalaemia, U have no Pot and no T, but a long PR and a long QT

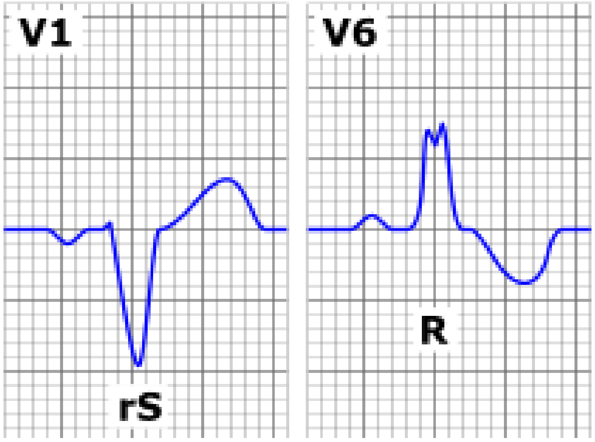
## ECG: HYPOTHERMIA

The following ECG changes may be seen in hypothermia
- bradycardia
- 'J' wave - small hump at the end of the QRS complex

- first degree heart block
- long QT interval
- atrial and ventricular arrhythmias

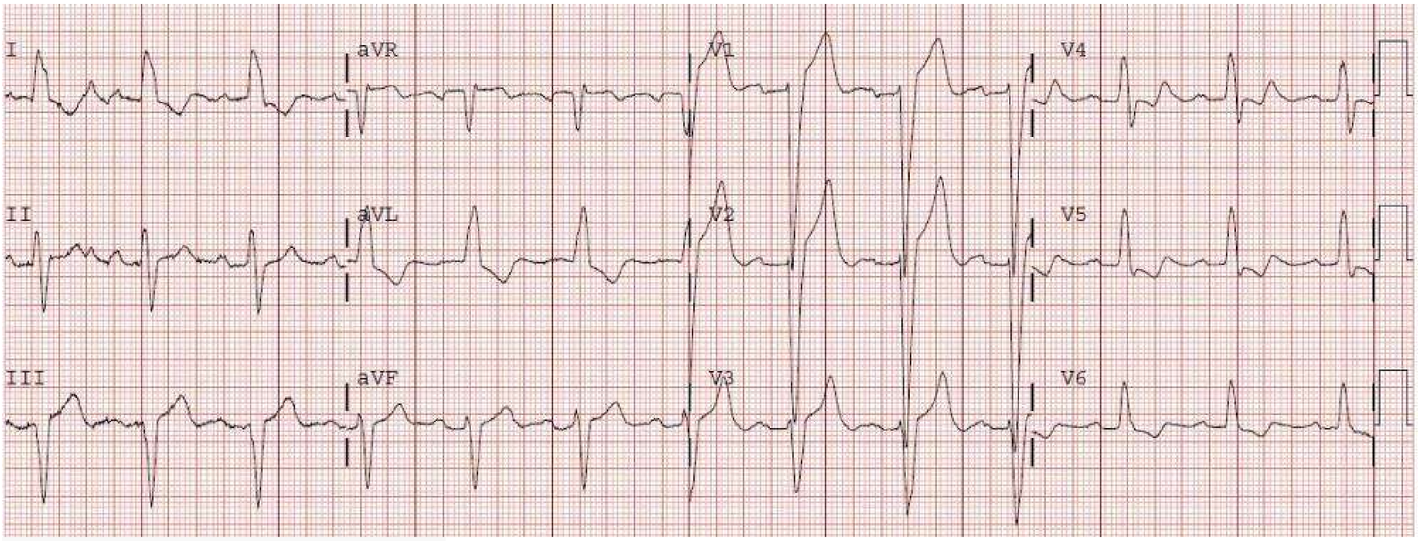
## ECG: LEFT BUNDLE BRANCH BLOCK

The diagram below shows the typical features of left bundle branch block (LBBB):



One of the most common ways to remember the difference between LBBB and RBBB is WiLLiaM MaRRoW

- in LBBB there is a 'W' in V1 and a 'M' in V6
- in RBBB there is a 'M' in V1 and a 'W' in V6



ECG showing typical features of LBBB

Causes of LBBB

- ischaemic heart disease
- hypertension
- aortic stenosis
- cardiomyopathy
- rare: idiopathic fibrosis, digoxin toxicity, hyperkalaemia

New LBBB is always pathological and may be a sign of a myocardial infarction. Diagnosing a myocardial infarction for patients with existing LBBB is difficult. The Sgarbossa criteria can help with this. Please see the link for more details.

## ECG: NORMAL VARIANTS

The following ECG changes are considered normal variants in an athlete:
- sinus bradycardia
- junctional rhythm
- first degree heart block
- Wenckebach phenomenon

## ECG: P WAVE CHANGES

Increased P wave amplitude
- cor pulmonale

## ECG: PR INTERVAL

Causes of a **prolonged PR interval**
- idiopathic
- ischaemic heart disease
- digoxin toxicity
- hypokalaemia*
- rheumatic fever
- aortic root pathology e.g. abscess secondary to endocarditis

- Lyme disease
- sarcoidosis
- myotonic dystrophy

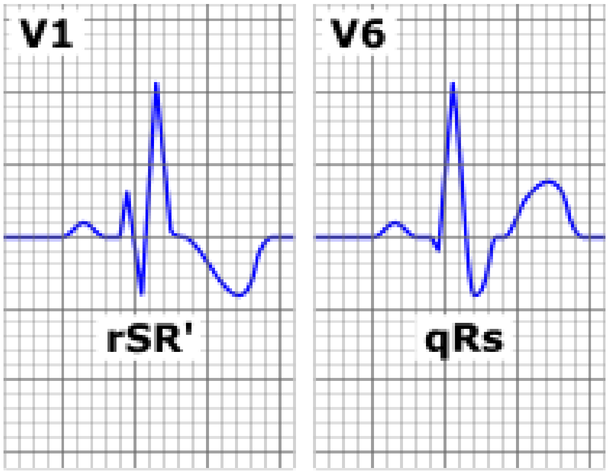
A prolonged PR interval may also be seen in athletes

A **short PR interval** is seen in Wolff-Parkinson-White syndrome

*hyperkalaemia can rarely cause a prolonged PR interval, but this is a much less common association than hypokalaemia

## ECG: RIGHT BUNDLE BRANCH BLOCK

Right bundle branch block is a common feature seen on ECGs.



One of the most common ways to remember the difference between LBBB and RBBB is WiLLiaM MaRRoW

- in LBBB there is a 'W' in V1 and a 'M' in V6
- in RBBB there is a 'M' in V1 and a 'W' in V6

Causes of RBBB

- normal variant - more common with increasing age
- right ventricular hypertrophy
- chronically increased right ventricular pressure - e.g. cor pulmonale
- pulmonary embolism

- myocardial infarction
- atrial septal defect (ostium secundum)
- cardiomyopathy or myocarditis

# ECG: ST DEPRESSION

Causes of ST depression
- secondary to abnormal QRS (LVH, LBBB, RBBB)
- ischaemia
- digoxin
- hypokalaemia
- syndrome X

# ECG: ST ELEVATION

Causes of ST elevation
- myocardial infarction
- pericarditis/myocarditis
- normal variant - 'high take-off'
- left ventricular aneurysm
- Prinzmetal's angina (coronary artery spasm)
- Takotsubo cardiomyopathy
- rare: subarachnoid haemorrhage

# ECG: T WAVE CHANGES

Peaked T waves
- hyperkalaemia
- myocardial ischaemia

Inverted T waves
- myocardial ischaemia

- digoxin toxicity
- subarachnoid haemorrhage
- arrhythmogenic right ventricular cardiomyopathy
- pulmonary embolism ('S1Q3T3')
- Brugada syndrome

## LONG QT SYNDROME

Long QT syndrome (LQTS) is an inherited condition associated with delayed repolarization of the ventricles. It is important to recognise as it may lead to ventricular tachycardia/torsade de pointes and can therefore cause collapse/sudden death. The most common variants of LQTS (LQT1 & LQT2) are caused by defects in the alpha subunit of the slow delayed rectifier potassium channel. A normal corrected QT interval is less than 430 ms in males and 450 ms in females.

Causes of a prolonged QT interval:

| Congenital | Drugs* | Other |
|---|---|---|
| • Jervell-Lange-Nielsen syndrome (includes deafness and is due to an abnormal potassium channel)<br>• Romano-Ward syndrome (no deafness) | ⍰ amiodarone, sotalol, class 1a antiarrhythmic drugs<br>⍰ tricyclic antidepressants, selective serotonin reuptake inhibitors (especially citalopram)<br>⍰ methadone<br>⍰ chloroquine<br>⍰ terfenadine**<br>⍰ erythromycin<br>⍰ haloperidol<br>⍰ ondanestron | ⍰ electrolyte: hypocalcaemia, hypokalaemia, hypomagnesaemia<br>⍰ acute myocardial infarction<br>⍰ myocarditis<br>⍰ hypothermia<br>⍰ subarachnoid haemorrhage |

Features

- may be picked up on routine ECG or following family screening
- Long QT1 - usually associated with exertional syncope, often swimming
- Long QT2 - often associated with syncope occurring following emotional stress, exercise or auditory stimuli
- Long QT3 - events often occur at night or at rest
- sudden cardiac death

Management
- avoid drugs which prolong the QT interval and other precipitants if appropriate (e.g. Strenuous exercise)
- beta-blockers***
- implantable cardioverter defibrillators in high risk cases

*the usual mechanism by which drugs prolong the QT interval is blockage of potassium channels. See the link for more details

**a non-sedating antihistamine and classic cause of prolonged QT in a patient, especially if also taking P450 enzyme inhibitor, e.g. Patient with a cold takes terfenadine and erythromycin at the same time

***note sotalol may exacerbate long QT syndrome

## IMPLANTABLE CARDIAC DEFIBRILLATORS

Indications
- long QT syndrome
- hypertrophic obstructive cardiomyopathy
- previous cardiac arrest due to VT/VF
- previous myocardial infarction with non-sustained VT on 24 hr monitoring, inducible VT on electrophysiology testing and ejection fraction < 35%
- Brugada syndrome

## TORSADES DE POINTES

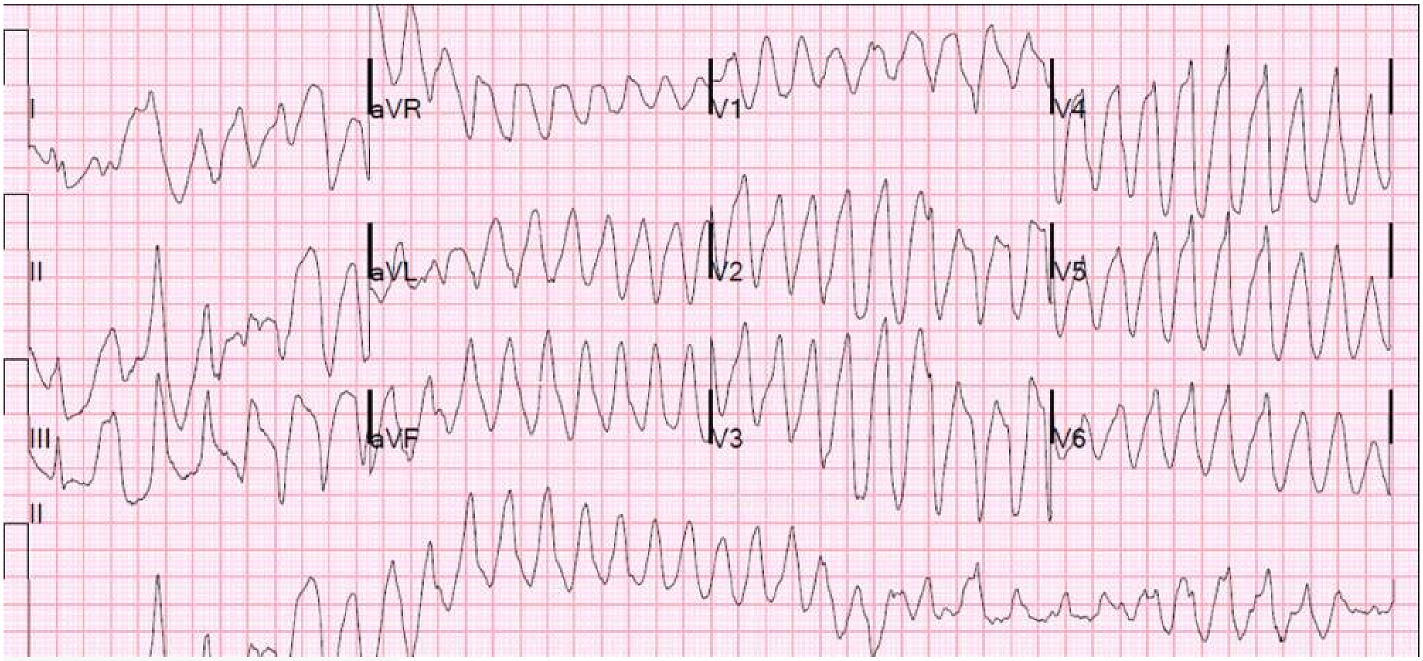
Torsades de pointes ('twisting of the points') is a form of polymorphic ventricular tachycardia associated with a long QT interval. It may deteriorate into ventricular fibrillation and hence lead to sudden death.

Causes of long QT interval
- congenital: Jervell-Lange-Nielsen syndrome, Romano-Ward syndrome

- antiarrhythmics: amiodarone, sotalol, class 1a antiarrhythmic drugs
- tricyclic antidepressants
- antipsychotics
- chloroquine
- terfenadine
- erythromycin
- electrolyte: hypocalcaemia, hypokalaemia, hypomagnesaemia
- myocarditis
- hypothermia
- subarachnoid haemorrhage

Management

- IV magnesium sulphate



ECG showing torsades de pointes

# PRE-ECLAMPSIA

Pre-eclampsia is a condition seen after 20 weeks gestation characterised by pregnancy-induced hypertension in association with proteinuria (> 0.3g / 24 hours). Oedema used to be third element of the classic triad but is now often not included in the definition as it is not specific

Pre-eclampsia is important as it predisposes to the following problems

- fetal: prematurity, intrauterine growth retardation
- eclampsia
- haemorrhage: placental abruption, intra-abdominal, intra-cerebral
- cardiac failure
- multi-organ failure

NICE divide risk factors into high and moderate risk:

| **High risk factors** | **Moderate risk factors** |
|---|---|
| • hypertensive disease in a previous pregnancy<br>• chronic kidney disease<br>• autoimmune disease, such as systemic lupus erythematosus or antiphospholipid syndrome<br>• type 1 or type 2 diabetes<br>• chronic hypertension | • first pregnancy<br>• age 40 years or older<br>• pregnancy interval of more than 10 years<br>• body mass index (BMI) of 35 kg/$m^2$ or more at first visit<br>• family history of pre-eclampsia<br>• multiple pregnancy |

Features of severe pre-eclampsia

- hypertension: typically > 170/110 mmHg and proteinuria as above
- proteinuria: dipstick ++/+++
- headache
- visual disturbance
- papilloedema
- RUQ/epigastric pain
- hyperreflexia
- platelet count < 100 * 106/l, abnormal liver enzymes or HELLP syndrome

Management

- consensus guidelines recommend treating blood pressure > 160/110 mmHg although many clinicians have a lower threshold
- oral labetalol is now first-line following the 2010 NICE guidelines. Nifedipine and hydralazine may also be used
- delivery of the baby is the most important and definitive management step. The timing depends on the individual clinical scenario

## ECLAMPSIA

Eclampsia may be defined as the development of seizures in association pre-eclampsia. To recap, pre-eclampsia is defined as:

- condition seen after 20 weeks gestation
- pregnancy-induced hypertension
- proteinuria

Magnesium sulphate is used to both prevent seizures in patients with severe pre-eclampsia and treat seizures once they develop. Guidelines on its use suggest the following:

- should be given once a decision to deliver has been made
- in eclampsia an IV bolus of 4g over 5-10 minutes should be given followed by an infusion of 1g / hour
- urine output, reflexes, respiratory rate and oxygen saturations should be monitored during treatment
    - respiratory depression can occur: calcium gluconate is the first-line treatment for magnesium sulphate induced respiratory depression
- treatment should continue for 24 hours after last seizure or delivery (around 40% of seizures occur post-partum)

Other important aspects of treating severe pre-eclampsia/eclampsia include fluid restriction to avoid the potentially serious consequences of fluid overload

# EXERCISE: PHYSIOLOGICAL CHANGES

Blood pressure

- systolic increases, diastolic decreases
- leads to increased pulse pressure
- in healthy young people the increase in MABP is only slight

Cardiac output

- increase in cardiac output may be 3-5 fold
- results from venous constriction, vasodilation and increased myocardial contractibility, as well as from the maintenance of right atrial pressure by an increase in venous return
- heart rate up to 3-fold increase
- stroke volume up to 1.5-fold increase

Systemic vascular resistance falls in exercise due to vasodilatation in active skeletal muscles.

# EXERCISE TOLERANCE TESTS

Exercise tolerance tests (ETT, also exercise ECG) are used for a variety of indications:

- assessing patients with suspected angina - however the 2010 NICE Chest pain of recent onset guidelines do not support the use of ETTs for all patients
- risk stratifying patients following a myocardial infarction
- assessing exercise tolerance
- risk stratifying patients with hypertrophic cardiomyopathy

ETT has a sensitivity of around 80% and a specificity of 70% for ischaemic heart disease.

Heart rate:

- maximum predicted heart rate = 220 - patient's age
- the target heart rate is at least 85% of maximum predicted to allow reasonable interpretation of
- a test as low-risk or negative

Contraindications

- myocardial infarction less than 7 days ago
- unstable angina
- uncontrolled hypertension (systolic BP > 180 mmHg) or hypotension (systolic BP < 90 mmHg)
- aortic stenosis
- left bundle branch block: this would make the ECG very difficult to interpret

Stop if:

- exhaustion / patient request
- 'severe', 'limiting' chest pain
- > 3mm ST depression
- > 2mm ST elevation.  Stop if rapid ST elevation and pain
- systolic blood pressure > 230 mmHg
- systolic blood pressure falling > 20 mmHg
- attainment of maximum predicted heart rate
- heart rate falling > 20% of starting rate
- arrhythmia develops

## HEART FAILURE: NYHA CLASSIFICATION

The New York Heart Association (NYHA) classification is widely used to classify the severity of heart failure:

NYHA Class I
- no symptoms
- no limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations

NYHA Class II
- mild symptoms
- slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations or dyspnoea

NYHA Class III
- moderate symptoms
- marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms

NYHA Class IV
- severe symptoms
- unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity

## CHRONIC HEART FAILURE: DIAGNOSIS

NICE issued updated guidelines on diagnosis and management in 2018. Previously the first-line investigation was determined by whether the patient has previously had a myocardial infarction or not this is no longer the case - all patients should have an N-terminal pro-B-type natriuretic peptide (NT-proBNP) blood test first-line.

Interpreting the test
- if levels are 'high' arrange specialist assessment (including transthoracic echocardiography) within 2 weeks

- if levels are 'raised' arrange specialist assessment (including transthoracic echocardiography) echocardiogram within 6 weeks

**Serum natriuretic peptides**
B-type natriuretic peptide (BNP) is a hormone produced mainly by the left ventricular myocardium in response to strain. Very high levels are associated with a poor prognosis.

| | BNP | NTproBNP |
|---|---|---|
| **High levels** | > 400 pg/ml (116 pmol/litre) | > 2000 pg/ml (236 pmol/litre) |
| **Raised levels** | 100-400 pg/ml (29-116 pmol/litre) | 400-2000 pg/ml (47-236 pmol/litre) |
| **Normal levels** | < 100 pg/ml (29 pmol/litre) | < 400 pg/ml (47 pmol/litre) |

Factors which alter the BNP level:

| Increase BNP levels | Decrease BNP levels |
|---|---|
| Left ventricular hypertrophy<br>Ischaemia<br>Tachycardia<br>Right ventricular overload<br>Hypoxaemia (including pulmonary embolism)<br>GFR < 60 ml/min<br>Sepsis<br>COPD<br>Diabetes<br>Age > 70<br>Liver cirrhosis | Obesity<br>Diuretics<br>ACE inhibitors<br>Beta-blockers<br>Angiotensin 2 receptor blockers<br>Aldosterone antagonists |

# B-TYPE NATRIURETIC PEPTIDE

B-type natriuretic peptide (BNP) is a hormone produced mainly by the left ventricular myocardium in response to strain.

Whilst heart failure is the most obvious cause of raised BNP levels any cause of left ventricular dysfunction such as myocardial ischaemia or valvular disease may raise levels. Raised levels may also be seen due to reduced excretion in patients with chronic kidney disease. Factors which reduce BNP levels include treatment with ACE inhibitors, angiotensin-2 receptor blockers and diuretics.

Effects of BNP

- vasodilator
- diuretic and natriuretic
- suppresses both sympathetic tone and the renin-angiotensin-aldosterone system

**Clinical uses of BNP**

Diagnosing patients with acute dyspnoea

- a low concentration of BNP(< 100pg/ml) makes a diagnosis of heart failure unlikely, but raised levels should prompt further investigation to confirm the diagnosis
- NICE currently recommends BNP as a helpful test to rule out a diagnosis of heart failure

Prognosis in patients with chronic heart failure

- initial evidence suggests BNP is an extremely useful marker of prognosis

Guiding treatment in patients with chronic heart failure

- effective treatment lowers BNP levels

Screening for cardiac dysfunction

- not currently recommended for population screening

## PULMONARY CAPILLARY WEDGE PRESSURE

Pulmonary capillary wedge pressure (PCWP) is measured using a balloon tipped Swan-Ganz catheter which is inserted into the pulmonary artery. The pressure measured is similar to that of the left atrium (normally 6-12 mmHg).

One of the main uses of measuring the PCWP is determining whether pulmonary oedema is caused by either heart failure or acute respiratory distress syndrome.

In many modern ITU departments PCWP measurement has been replaced by non-invasive techniques.

# HEART FAILURE: NON-DRUG MANAGEMENT

Cardiac resynchronisation therapy
- for patients with heart failure and wide QRS
- biventricular pacing
- improved symptoms and reduced hospitalisation in NYHA class III patients

Exercise training
- improves symptoms but not hospitalisation/mortality

# HEART FAILURE: DRUG MANAGEMENT

A number of drugs have been shown to improve mortality in patients with chronic heart failure:
- ACE inhibitors (SAVE, SOLVD, CONSENSUS)
- spironolactone (RALES)
- beta-blockers (CIBIS)
- hydralazine with nitrates (VHEFT-1)

No long-term reduction in mortality has been demonstrated for loop diuretics such as furosemide.

NICE issued updated guidelines on management in 2010, key points include:
- first-line treatment for all patients is both an **ACE-inhibitor** and a **beta-blocker***. Generally, one drug should be started at a time
- second-line treatment is now either an **aldosterone antagonist**, angiotensin II receptor blocker or a hydralazine in combination with a nitrate
- if symptoms persist **cardiac resynchronisation therapy** or **digoxin**** should be considered. An alternative supported by NICE in 2012 is ivabradine. The criteria for **ivabradine** include that the patient is already on suitable therapy (ACE-inhibitor, beta-blocker + aldosterone antagonist), has a heart rate > 75/min and a left ventricular fraction < 35%
- **diuretics** should be given for fluid overload

- offer **annual influenza vaccine**
- offer one-off*** **pneumococcal vaccine**

Other drugs

- sacubitril-valsartan is considered in heart failure with reduced ejection fraction who are symptomatic on ACE inhibitors or ARBs
- sacubitril-valsartan should be initiated following ACEi or ARB wash-out period

Beta-blockers licensed to treat heart failure in the UK include bisoprolol, carvedilol, and nebivolol.

*ACE-inhibitors and beta-blockers have no effect on mortality in heart failure with preserved ejection fraction

**digoxin has also not been proven to reduce mortality in patients with heart failure. It may however improve symptoms due to its inotropic properties. Digoxin is strongly indicated if there is coexistent atrial fibrillation

***adults usually require just one dose but those with asplenia, splenic dysfunction or chronic kidney disease need a booster every 5 years

# HEART SOUNDS

The first heart sound (S1) is caused by closure of the mitral and tricuspid valves whilst the second heart sound (S2) is due to aortic and pulmonary valve closure

S1
- closure of mitral and tricuspid valves
- soft if long PR or mitral regurgitation
- loud in mitral stenosis

S2
- closure of aortic and pulmonary valves
- soft in aortic stenosis
- splitting during inspiration is normal

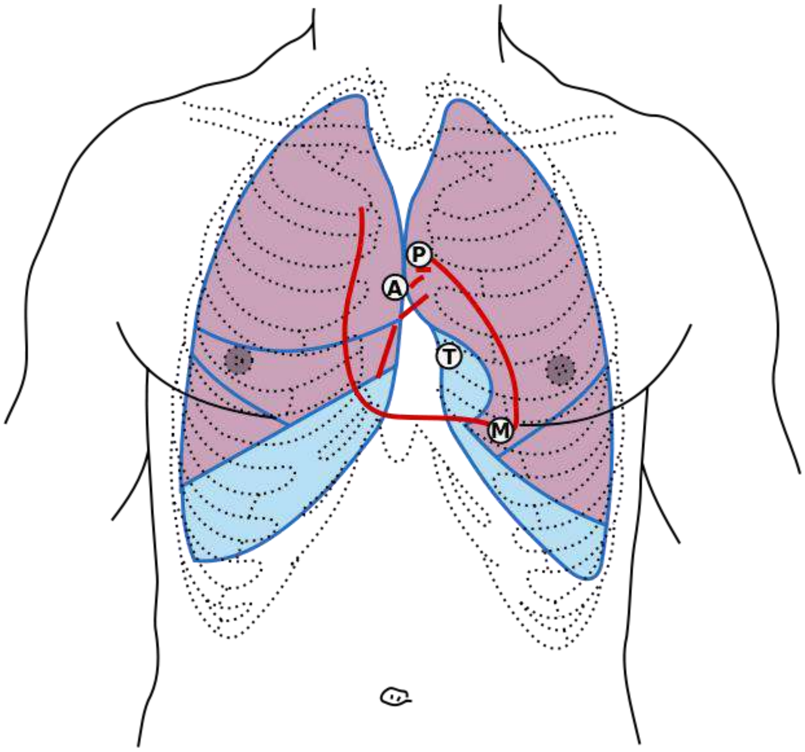
S3 (third heart sound)
- caused by diastolic filling of the ventricle
- considered normal if < 30 years old (may persist in women up to 50 years old)
- heard in left ventricular failure (e.g. dilated cardiomyopathy), constrictive pericarditis (called a pericardial knock) and mitral regurgitation

S4 (fourth heart sound)
- may be heard in aortic stenosis, HOCM, hypertension
- caused by atrial contraction against a stiff ventricle
- therefore coincides with the P wave on ECG
- in HOCM a double apical impulse may be felt as a result of a palpable S4

## Sites of auscultation

| Valve | Site |
|---|---|
| Pulmonary valve | Left second intercostal space, at the upper sternal border |
| Aortic valve | Right second intercostal space, at the upper sternal border |
| Mitral valve | Left fifth intercostal space, just medial to mid clavicular line |
| Tricuspid valve | Left fourth intercostal space, at the lower left sternal border |

The diagram below demonstrates where the various cardiac valves are best heard.



## HEART SOUNDS: S1

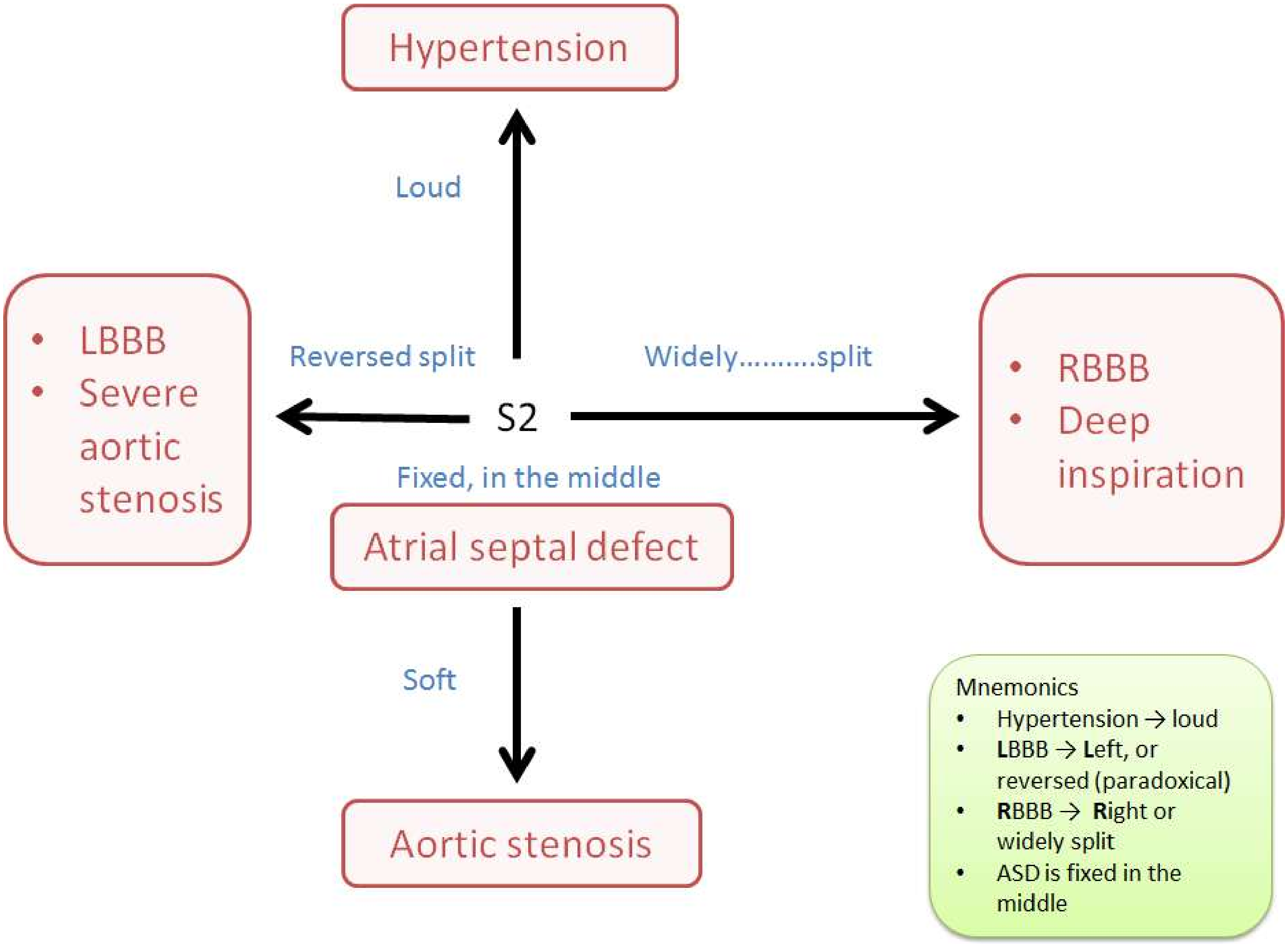
S1 is caused by closure of mitral and tricuspid valves

Causes of a loud S1
- mitral stenosis
- left-to-right shunts
- short PR interval, atrial premature beats
- hyperdynamic states

Causes of a quiet S1
mitral regurgitation

## HEART SOUNDS: S2

S2 is caused by the closure of the aortic valve (A2) closely followed by that of the pulmonary valve (P2)


Hypertension
Loud
Reversed split
Widely..........split
S2
Fixed, in the middle
LBBB
Severe aortic stenosis
RBBB
Deep inspiration
Atrial septal defect
Soft
Aortic stenosis

Mnemonics

- Hypertension → loud
- **L**BBB → **L**eft, or reversed (paradoxical)
- **R**BBB → **R**ight or widely split
- ASD is fixed in the middle

Causes of a loud S2

- hypertension: systemic (loud A2) or pulmonary (loud P2)
- hyperdynamic states
- atrial septal defect without pulmonary hypertension

Causes of a soft S2

- aortic stenosis

Causes of fixed split S2

- atrial septal defect

Causes of a widely split S2

- deep inspiration
- RBBB

- pulmonary stenosis
- severe mitral regurgitation

Causes of a reversed (paradoxical) split S2 (P2 occurs before A2)
- LBBB
- severe aortic stenosis
- right ventricular pacing
- WPW type B (causes early P2)
- patent ductus arteriosus

## MURMURS

Ejection systolic
- aortic stenosis
- pulmonary stenosis, hypertrophic obstructive cardiomyopathy
- atrial septal defect, tetralogy of Fallot

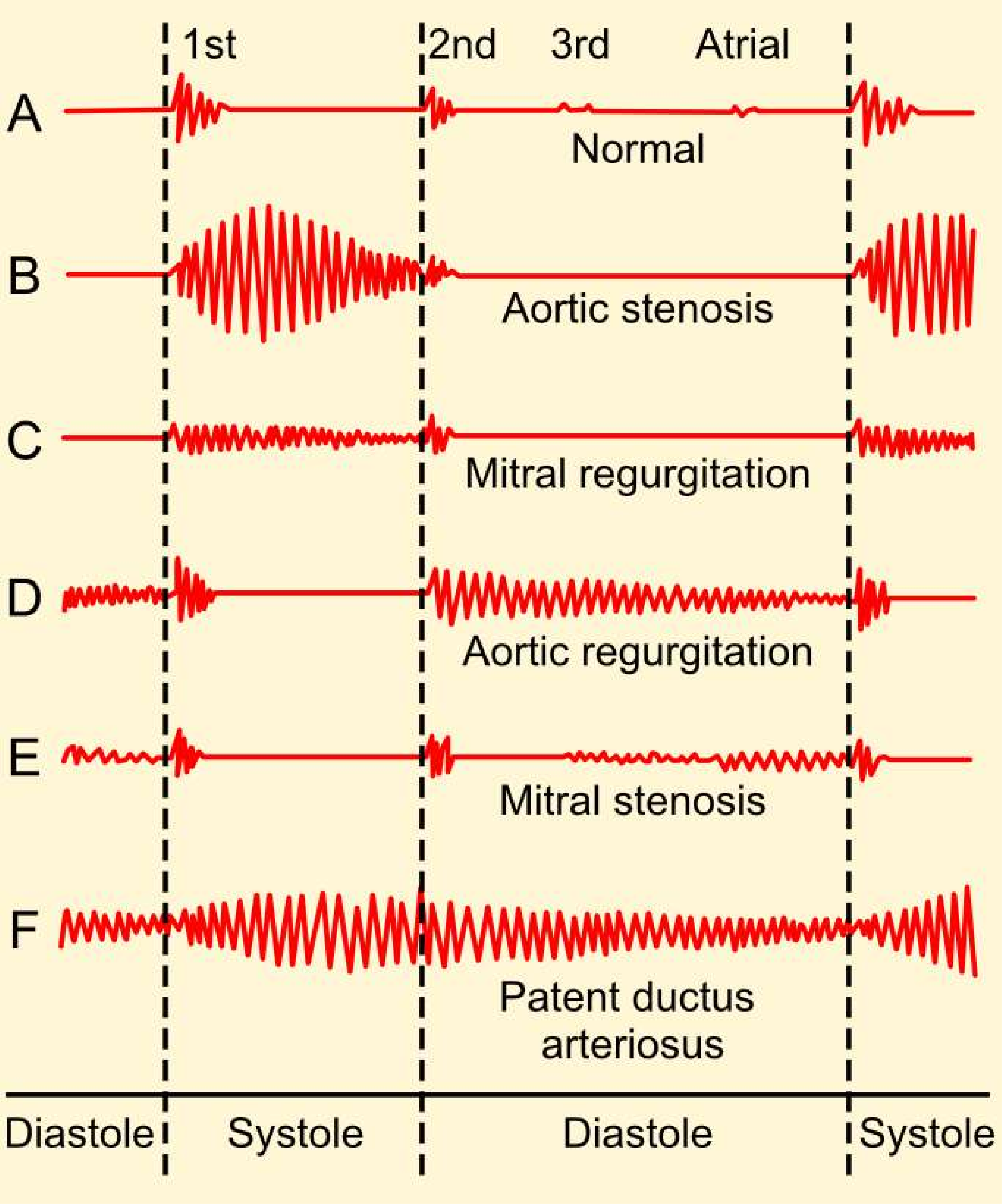
Holosystolic (pansystolic)
- mitral/tricuspid regurgitation (high-pitched and 'blowing' in character)
- ventricular septal defect ('harsh' in character)

Late systolic
- mitral valve prolapse
- coarctation of aorta

Early diastolic
- aortic regurgitation (high-pitched and 'blowing' in character)
- Graham-Steel murmur (pulmonary regurgitation, again high-pitched and 'blowing' in character)

Mid-late diastolic
- mitral stenosis ('rumbling' in character)
- Austin-Flint murmur (severe aortic regurgitation, again is 'rumbling' in character)

Continuous machine-like murmur
- patent ductus arteriosus


1st
2nd
3rd
Atrial
A
Normal
B
Aortic stenosis
C
Mitral regurgitation
D
Aortic regurgitation
E
Mitral stenosis
F
Patent ductus arteriosus
Diastole
Systole
Diastole
Systole

# INVESTIGATING PALPITATIONS

Palpitations are a common presenting symptom.

Possible causes include
- arrhythmias
- stress
- increased awareness of normal heart beat / extrasystoles

First-line investigations include:
- 12-lead ECG: this will only capture the heart rhythm for a few seconds and hence is likely to miss episodic arrhythmias. However, other abnormalities linked to the underlying arrhythmia (for example a prolonged QT interval or PR interval, or changes suggesting recent myocardial ischaemia) may be seen.
- thyroid function tests: thyrotoxicosis may precipitate atrial fibrillation and other arrhythmias
- urea and electrolytes: looking for disturbances such as a low potassium
- full blood count

**Capturing episodic arrhythmias**
First-line investigations are often normal in patients complaining of palpitations. The next step is to exclude an episode arrhythmia.

The most common investigation is Holter monitoring
- portable battery operated device
- continuously records ECG from 2-3 leads
- usually done for 24 hours but may be used for longer if symptoms are less than daily
- patients are asked to keep a diary to record any symptomatic palpitations. This can later be compared to the rhythm strip at the time of the symptoms
- at the end of the monitoring a report is generated summarising a number of parameters including heart rate, arrhythmias and changes in ECG waveform

If no abnormality is found on the Holter monitor, and symptoms continue, other options include:
- external loop recorder
- implantable loop recorder

# PULSES

Pulsus paradoxus
- greater than the normal (10 mmHg) fall in systolic blood pressure during inspiration → faint or absent pulse in inspiration
- severe asthma, cardiac tamponade

Slow-rising/plateau
- aortic stenosis

Collapsing
- aortic regurgitation
- patent ductus arteriosus
- hyperkinetic states (anaemia, thyrotoxic, fever, exercise/pregnancy)

Pulsus alternans
- regular alternation of the force of the arterial pulse
- severe LVF

Bisferiens pulse
- 'double pulse' - two systolic peaks
- mixed aortic valve disease

'Jerky' pulse
- hypertrophic obstructive cardiomyopathy*

*HOCM may occasionally be associated with a bisferiens pulse

# HYPERLIPIDAEMIA: XANTHOMATA

Characteristic xanthomata seen in hyperlipidaemia:

Palmar xanthoma
- remnant hyperlipidaemia
- may less commonly be seen in familial hypercholesterolaemia

Eruptive xanthoma are due to high triglyceride levels and present as multiple red/yellow vesicles on the extensor surfaces (e.g. elbows, knees)

Causes of eruptive xanthoma
- familial hypertriglyceridaemia
- lipoprotein lipase deficiency

Tendon xanthoma, tuberous xanthoma, xanthelasma
- familial hypercholesterolaemia
- remnant hyperlipidaemia

Xanthelasma are also seen without lipid abnormalities

Management of xanthelasma, options include:
- surgical excision
- topical trichloroacetic acid
- laser therapy
- electrodesiccation

# STATINS

Statins inhibit the action of HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis.

Adverse effects
- myopathy: includes myalgia, myositis, rhabdomyolysis and asymptomatic raised creatine kinase. Risks factors for myopathy include advanced age, female sex, low

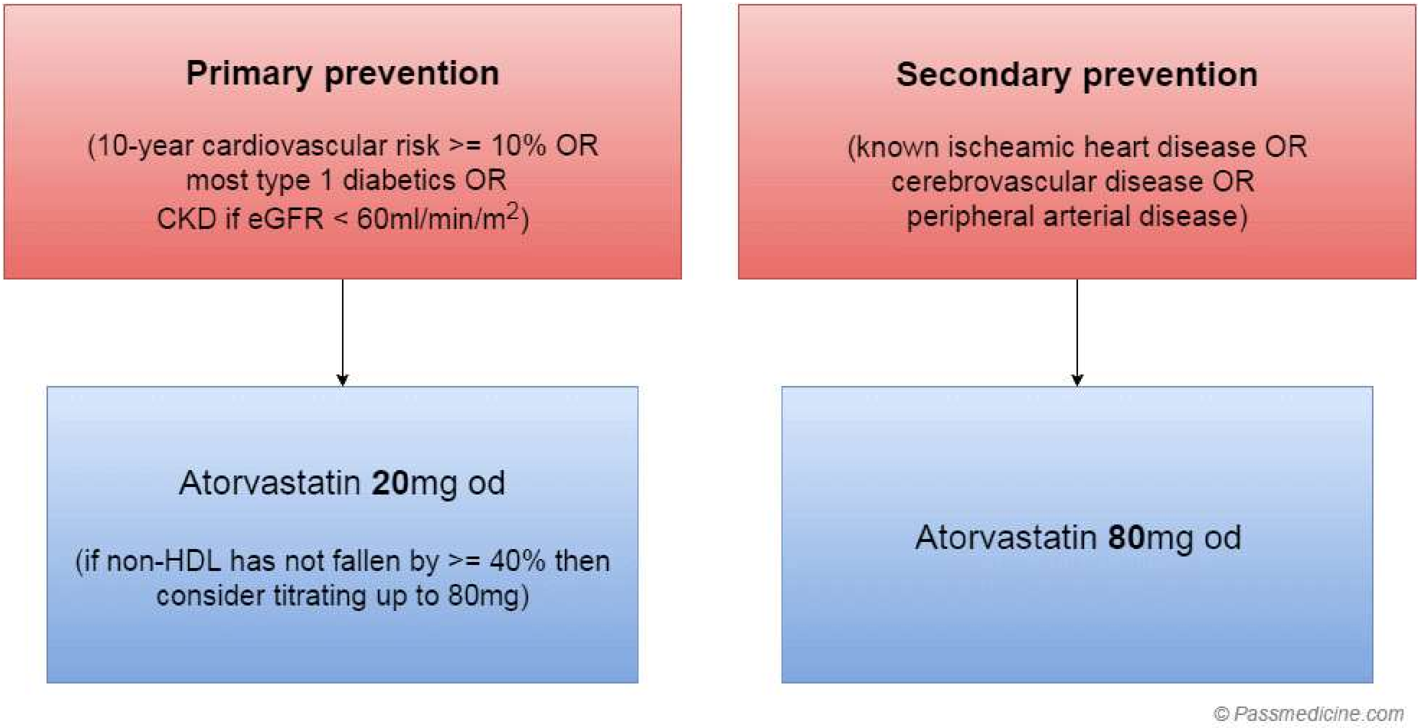
body mass index and presence of multisystem disease such as diabetes mellitus. Myopathy is more common in lipophilic statins (simvastatin, atorvastatin) than relatively hydrophilic statins (rosuvastatin, pravastatin, fluvastatin)
- liver impairment: the 2014 NICE guidelines recommend checking LFTs at baseline, 3 months and 12 months. Treatment should be discontinued if serum transaminase concentrations rise to and persist at 3 times the upper limit of the reference range
- there is some evidence that statins may increase the risk of intracerebral haemorrhage in patients who've previously had a stroke. This effect is not seen in primary prevention. For this reason the Royal College of Physicians recommend avoiding statins in patients with a history of intracerebral haemorrhage

Contraindications
- macrolides (e.g. erythromycin, clarithromycin) are an important interaction. Statins should be stopped until patients complete the course
- pregnancy

Who should receive a statin?
- all people with established cardiovascular disease (stroke, TIA, ischaemic heart disease, peripheral arterial disease)
- following the 2014 update, NICE recommend anyone with a 10-year cardiovascular risk >= 10%
- patients with type 2 diabetes mellitus should now be assessed using QRISK2 like other patients are, to determine whether they should be started on statins
- patients with type 1 diabetes mellitus who were diagnosed more than 10 years ago OR are aged over 40 OR have established nephropathy

Statins should be taken at night as this is when the majority of cholesterol synthesis takes place. This is especially true for simvastatin which has a shorter half-life than other statins.

NICE currently recommends the following for the prevention of cardiovascular disease:
- atorvastatin 20mg for primary prevention
  - increase the dose if non-HDL has not reduced for >= 40%
- atorvastatin 80mg for secondary prevention


Primary prevention
(10-year cardiovascular risk >= 10% OR most type 1 diabetics OR CKD if eGFR < 60ml/min/m2)
Secondary prevention
(known ischeamic heart disease OR cerebrovascular disease OR peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

## NICOTINIC ACID

Nicotinic acid (niacin) is used in the treatment of patients with hyperlipidaemia, although its use is limited by side-effects. As well as lowering cholesterol and triglyceride concentrations it also raises HDL levels.

Adverse effects
- flushing: mediated by prostaglandins
- impaired glucose tolerance
- myositis

## HYPERCALCAEMIA: FEATURES

Features
- 'bones, stones, groans and psychic moans'
- corneal calcification
- shortened QT interval on ECG
- hypertension

# BLOOD PRESSURE MEASUREMENT

As blood pressure (BP) is one of the main physiological measurements taken in medicine it is important to ensure the values are accurate. Many of the following points apply to electronic sphygmomanometers as well.

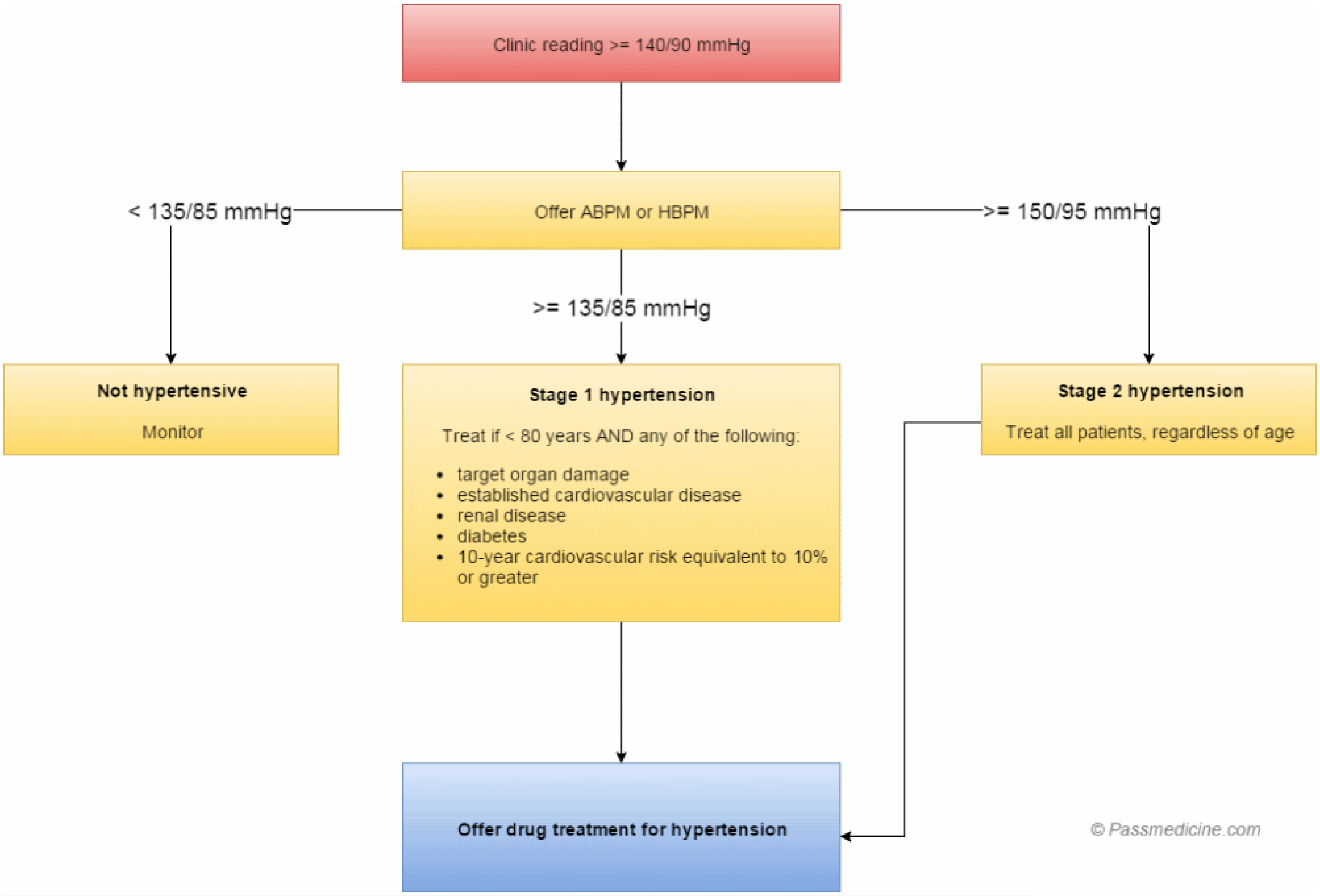
Reasons for inaccurate values:
- wrong cuff size: bladder too small: overestimation of BP. Bladder too large: underestimation of BP
- the arm should be horizontal at the level of the heart. Lowering of the arm below heart level: overestimation of BP. Elevation of the arm above heart level: underestimation of BP
- posture: the sitting position is considered standard for routine BP measurement.
- arm support: if the arm is unsupported this may raise the diastolic blood pressure (as the arm is performing isometric exercise)

NICE recommends measuring blood pressure in both arms when considering a diagnosis of hypertension.

If the difference in readings between arms is more than 20 mmHg then the measurements should be repeated. If the difference remains > 20 mmHg then subsequent blood pressures should be recorded from the arm with the higher reading.

# HYPERTENSION: DIAGNOSIS

NICE published updated guidelines for the management of hypertension in 2019. This builds on the significant guidelines released in 2011 that recommended:
- classifying hypertension into stages
- recommending the use of ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM)


Clinic reading >= 140/90 mmHg
Offer ABPM or HBPM
< 135/85 mmHg
>= 135/85 mmHg
>= 150/95 mmHg
Not hypertensive
Monitor
Stage 1 hypertension
Treat if < 80 years AND any of the following:
target organ damage
established cardiovascular disease
renal disease
diabetes
10-year cardiovascular risk equivalent to 10% or greater
Stage 2 hypertension
Treat all patients, regardless of age
Offer drug treatment for hypertension
© Passmedicine.com

Flow chart showing simplified schematic for diagnosis hypertension following NICE guidelines

**Why were these guidelines needed?**

It has long been recognised by doctors that there is a subgroup of patients whose blood pressure climbs 20 mmHg whenever they enter a clinical setting, so called 'white coat hypertension'. If we just rely on clinic readings then such patients may be diagnosed as having hypertension when, the vast majority of the time, their blood pressure is normal.

This has led to the use of both ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM) to confirm the diagnosis of hypertension. These techniques allow a more accurate assessment of a patients' overall blood pressure. Not only does this help prevent overdiagnosis of hypertension - ABPM has been shown to be a more accurate predictor of cardiovascular events than clinic readings.

**Blood pressure classification**

This becomes relevant later in some of the management decisions that NICE advocate.

| Stage | Criteria |
|---|---|
| **Stage 1 hypertension** | Clinic BP >= 140/90 mmHg and subsequent ABPM daytime average or HBPM average BP >= 135/85 mmHg |
| **Stage 2 hypertension** | Clinic BP >= 160/100 mmHg and subsequent ABPM daytime average or HBPM average BP >= 150/95 mmHg |
| **Severe hypertension** | Clinic systolic BP >= 180 mmHg, or clinic diastolic BP >= 110 mmHg |

**Diagnosing hypertension**

Firstly, NICE recommend measuring blood pressure in both arms when considering a diagnosis of hypertension.

If the difference in readings between arms is more than 20 mmHg then the measurements should be repeated. If the difference remains > 20 mmHg then subsequent blood pressures should be recorded from the arm with the higher reading.

It should of course be remember that there are pathological causes of unequal blood pressure readings from the arms, such as supravalvular aortic stenosis. It is therefore prudent to listen to the heart sounds if a difference exists and further investigation if a very large difference is noted.

NICE also recommend taking a second reading during the consultation, if the first reading is > 140/90 mmHg. The lower reading of the two should determine further management.

NICE suggest offering ABPM or HBPM to any patient with a blood pressure >= 140/90 mmHg.

If however the blood pressure is >= 180/110 mmHg:
- immediate treatment should be considered
- if there are signs of papilloedema or retinal haemorrhages NICE recommend same day assessment by a specialist
- NICE also recommend referral if a phaeochromocytoma is suspected (labile or postural hypotension, headache, palpitations, pallor and diaphoresis)

Ambulatory blood pressure monitoring (ABPM)
- at least 2 measurements per hour during the person's usual waking hours (for example, between 08:00 and 22:00)
- use the average value of at least 14 measurements

If ABPM is not tolerated or declined HBPM should be offered.

Home blood pressure monitoring (HBPM)
- for each BP recording, two consecutive measurements need to be taken, at least 1 minute apart and with the person seated
- BP should be recorded twice daily, ideally in the morning and evening
- BP should be recorded for at least 4 days, ideally for 7 days
- discard the measurements taken on the first day and use the average value of all the remaining measurements

**Interpreting the results**
ABPM/HBPM >= 135/85 mmHg (i.e. stage 1 hypertension)
- treat if < 80 years of age AND any of the following apply; target organ damage, established cardiovascular disease, renal disease, diabetes or a 10-year cardiovascular risk equivalent to 10% or greater
- in 2019, NICE made a further recommendation, suggesting that we should 'consider antihypertensive drug treatment in addition to lifestyle advice for adults aged under 60 with stage 1 hypertension and an estimated 10-year risk below 10%. '. This seems to be due to evidence that QRISK may underestimate the lifetime probability of developing cardiovascular disease

ABPM/HBPM >= 150/95 mmHg (i.e. stage 2 hypertension)
- offer drug treatment regardless of age

# HYPERTENSION: SECONDARY CAUSES

It is thought that between 5-10% of patients diagnosed with hypertension have primary hyperaldosteronism, including Conn's syndrome. This makes it the single most common cause of secondary hypertension.

Renal disease accounts for a large percentage of the other cases of secondary hypertension. Conditions which may increase the blood pressure include:
- glomerulonephritis
- pyelonephritis
- adult polycystic kidney disease

- renal artery stenosis

Endocrine disorders (other than primary hyperaldosteronism) may also result in increased blood pressure:
- phaeochromocytoma
- Cushing's syndrome
- Liddle's syndrome
- congenital adrenal hyperplasia (11-beta hydroxylase deficiency)
- acromegaly

Drug causes:
- steroids
- monoamine oxidase inhibitors
- the combined oral contraceptive pill
- NSAIDs
- leflunomide

Other causes include:
- pregnancy
- coarctation of the aorta

# HYPERTENSION: MANAGEMENT

NICE published updated guidelines for the management of hypertension in 2019. Some of the key changes include:
- lowering the threshold for treating stage 1 hypertension in patients < 80 years from 20% to 10%
- angiotensin receptor blockers can be used instead of ACE-inhibitors where indicated
- if a patient is already taking an ACE-inhibitor or angiotensin receptor blocker, then a calcium channel blocker OR a thiazide-like diuretic can be used. Previously only a calcium channel blocker was recommended

**Blood pressure classification**
This becomes relevant later in some of the management decisions that NICE advocate.

| Stage | Criteria |
|---|---|
| **Stage 1 hypertension** | Clinic BP >= 140/90 mmHg and subsequent ABPM daytime average or HBPM average BP >= 135/85 mmHg |
| **Stage 2 hypertension** | Clinic BP >= 160/100 mmHg and subsequent ABPM daytime average or HBPM average BP >= 150/95 mmHg |
| **Severe hypertension** | Clinic systolic BP >= 180 mmHg, or clinic diastolic BP >= 110 mmHg |

**Managing hypertension**

Lifestyle advice should not be forgotten and is frequently tested in exams:

- a low salt diet is recommended, aiming for less than 6g/day, ideally 3g/day. The average adult in the UK consumes around 8-12g/day of salt. A recent BMJ paper* showed that lowering salt intake can have a significant effect on blood pressure. For example, reducing salt intake by 6g/day can lower systolic blood pressure by 10mmHg
- caffeine intake should be reduced
- the other general bits of advice remain: stop smoking, drink less alcohol, eat a balanced diet rich in fruit and vegetables, exercise more, lose weight

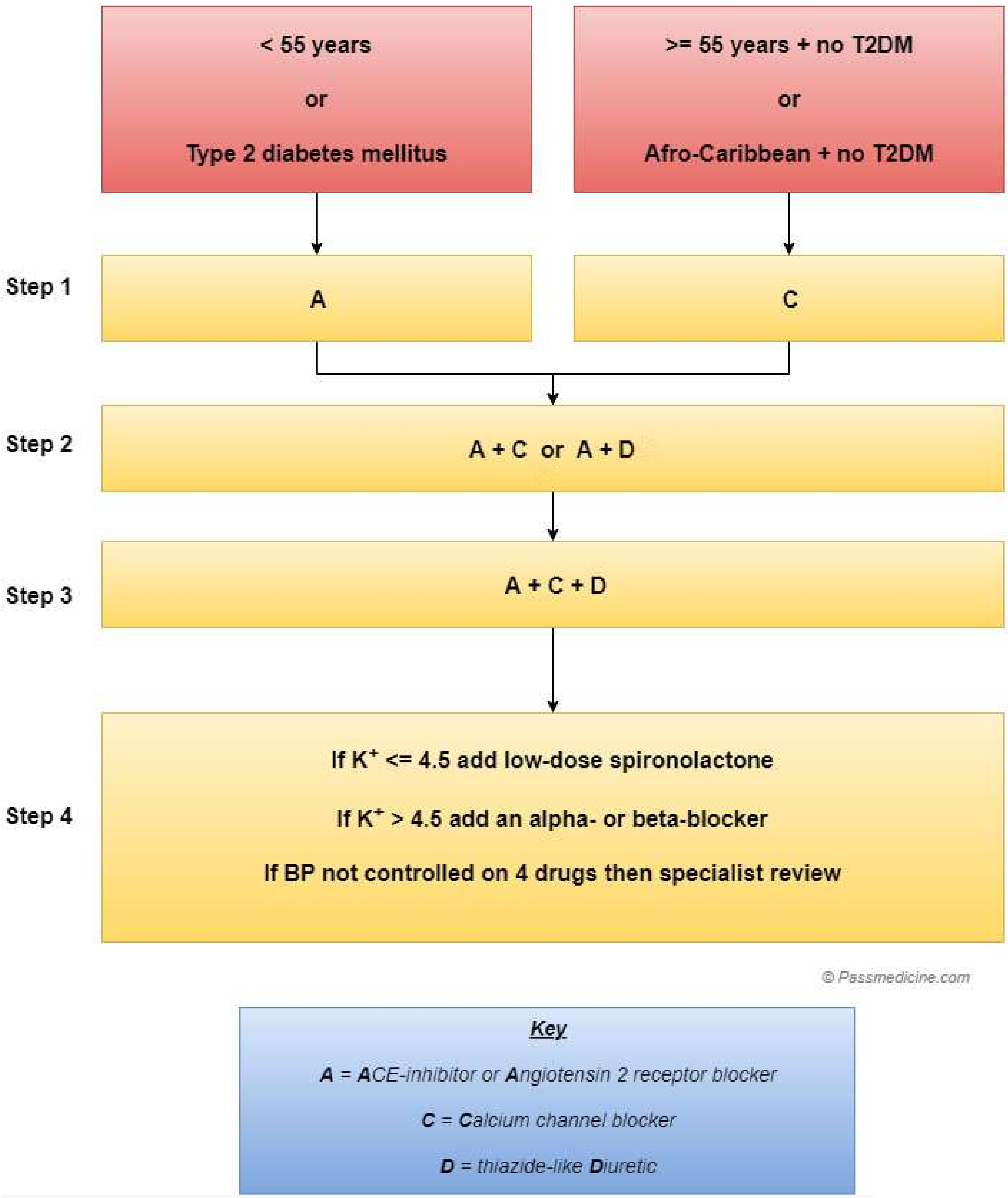
ABPM/HBPM >= 135/85 mmHg (i.e. stage 1 hypertension)

- treat if < 80 years of age AND any of the following apply; target organ damage, established cardiovascular disease, renal disease, diabetes or a 10-year cardiovascular risk equivalent to 10% or greater
- in 2019, NICE made a further recommendation, suggesting that we should 'consider antihypertensive drug treatment in addition to lifestyle advice for adults aged under 60 with stage 1 hypertension and an estimated 10-year risk below 10%. '. This seems to be due to evidence that QRISK may underestimate the lifetime probability of developing cardiovascular disease

ABPM/HBPM >= 150/95 mmHg (i.e. stage 2 hypertension)

- offer drug treatment regardless of age

For patients < 40 years consider specialist referral to exclude secondary causes.


< 55 years
or
Type 2 diabetes mellitus
>= 55 years + no T2DM
or
Afro-Caribbean + no T2DM
Step 1
A
C
Step 2
A + C or A + D
Step 3
A + C + D
Step 4
If $K^+$ <= 4.5 add low-dose spironolactone
If $K^+$ > 4.5 add an alpha- or beta-blocker
If BP not controlled on 4 drugs then specialist review
© Passmedicine.com
Key
A = ACE-inhibitor or Angiotensin 2 receptor blocker
C = Calcium channel blocker
D = thiazide-like Diuretic

Flow chart showing the management of hypertension as per current NICE guideliness

### Step 1 treatment

- patients < 55-years-old or a background of type 2 diabetes mellitus: **A**CE inhibitor or a **A**ngiotension receptor blocker (**A**CE-i or **A**RB): **(A)**
    - angiotensin receptor blockers should be used where ACE inhibitors are not tolerated (e.g. due to a cough)
- patients >= 55-years-old or of Afro-Caribbean origin: **C**alcium channel blocker **(C)**
    - ACE inhibitors have reduced efficacy in patients of Afro-Caribbean origin are therefore not used first-line

Step 2 treatment

- if already taking an **A**CE-i or **A**RB add a **C**alcium channel blocker or a thiazide-like Diuretic
- if already taking a **C**alcium channel blocker add an **A**CE-i or **A**RB
  - for patients of Afro-Caribbean origin taking a calcium channel blocker for hypertension, if they require a second agent consider an angiotensin receptor blocker in preference to an ACE inhibitor
- **(A + C) or (A + D)**

Step 3 treatment

- add a third drug to make, i.e.:
  - if already taking an **(A + C)** then add a **D**
  - if already **(A + D)** then add a **C**
- **(A + C + D)**

Step 4 treatment

- NICE define step 4 as resistant hypertension and suggest either adding a 4th drug (as below) or seeking specialist advice
- first, check for:
  - confirm elevated clinic BP with ABPM or HBPM
  - assess for postural hypotension.
  - discuss adherence
- if potassium < 4.5 mmol/l add low-dose spironolactone
- if potassium > 4.5 mmol/l add an alpha- or beta-blocker

Patients who fail to respond to step 4 measures should be referred to a specialist. NICE recommend:

*If blood pressure remains uncontrolled with the optimal or maximum tolerated doses of four drugs, seek expert advice if it has not yet been obtained.*

**Blood pressure targets**

| | Clinic BP | ABPM / HBPM |
|---|---|---|
| **Age < 80 years** | 140/90 mmHg | 135/85 mmHg |
| **Age > 80 years** | 150/90 mmHg | 145/85 mmHg |

**New drugs**

Direct renin inhibitors

- e.g. Aliskiren (branded as Rasilez)
- by inhibiting renin blocks the conversion of angiotensinogen to angiotensin I
- no trials have looked at mortality data yet. Trials have only investigated fall in blood pressure. Initial trials suggest aliskiren reduces blood pressure to a similar extent as angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor antagonists
- adverse effects were uncommon in trials although diarrhoea was occasionally seen
- only current role would seem to be in patients who are intolerant of more established antihypertensive drugs

*BMJ 2013;346:f1325

# ACE INHIBITORS

Angiotensin-converting enzyme (ACE) inhibitors are now the established first-line treatment in younger patients with hypertension and are also extensively used to treat heart failure. They are known to be less effective in treating hypertensive Afro-Caribbean patients. ACE inhibitors are also used to treat diabetic nephropathy and have a role in the secondary prevention of ischaemic heart disease.

Mechanism of action:

- inhibit the conversion angiotensin I to angiotensin II
- ACE inhibitors are activated by phase 1 metabolism in the liver

Side-effects:

- cough
  - occurs in around 15% of patients and may occur up to a year after starting treatment
  - thought to be due to increased bradykinin levels
- angioedema: may occur up to a year after starting treatment
- hyperkalaemia
- first-dose hypotension: more common in patients taking diuretics

Cautions and contraindications

- pregnancy and breastfeeding - avoid
- renovascular disease - significant renal impairment may occur in patients who have undiagnosed bilateral renal artery stenosis
- aortic stenosis - may result in hypotension
- hereditary of idiopathic angioedema
- specialist advice should be sought before starting ACE inhibitors in patients with a potassium >= 5.0 mmol/L

Interactions

- patients receiving high-dose diuretic therapy (more than 80 mg of furosemide a day)
  - significantly increases the risk of hypotension

Monitoring

- urea and electrolytes should be checked before treatment is initiated and after increasing the dose
- a rise in the creatinine and potassium may be expected after starting ACE inhibitors. Acceptable changes are an increase in serum creatinine, up to 30%* from baseline and an increase in potassium up to 5.5 mmol/l*.Isolated systolic hypertension (ISH) is common in the elderly, affecting around 50% of people older than 70 years old. The Systolic Hypertension in the Elderly Program (SHEP) back in 1991 established that treating ISH reduced both strokes and ischaemic heart disease. Drugs such as thiazides were recommended as first line agents. This approach is contradicated by the 2011 NICE guidelines which recommends treating ISH in the same stepwise fashion as standard hypertension.

*Renal Association UK, Clinical Knowledge Summaries quote 50% which seems rather high. SIGN advise that the fall in eGFR should be less than 20%. The NICE CKD guidelines suggest that a decrease in eGFR of up to 25% or a rise in creatinine of up to 30% is acceptable

## ACE INHIBITORS: SIDE-EFFECTS

Side-effects:

- cough: occurs in around 15% of patients and may occur up to a year after starting treatment. Thought to be due to increased bradykinin levels

- angioedema: may occur up to a year after starting treatment
- hyperkalaemia
- first-dose hypotension: more common in patients taking diuretics

Cautions and contraindications

- pregnancy and breastfeeding - avoid
- renovascular disease - significant renal impairment may occur in patients who have undiagnosed bilateral renal artery stenosis
- aortic stenosis - may result in hypotension
- patients receiving high-dose diuretic therapy (more than 80 mg of furosemide a day) - significantly increases the risk of hypotension
- hereditary of idiopathic angioedema

Monitoring

- urea and electrolytes should be checked before treatment is initiated and after increasing the dose
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*Renal Association UK, Clinical Knowledge Summaries quote 50% which seems rather high. SIGN advise that the fall in eGFR should be less than 20%. The NICE CKD guidelines suggest that a decrease in eGFR of up to 25% or a rise in creatinine of up to 30% is acceptable

## ANGIOTENSIN II RECEPTOR BLOCKERS

Angiotensin II receptor blockers are generally used in situations where patients have not tolerated an ACE inhibitor, usually due to the development of a cough.

Examples

- candesartan
- losartan
- irbesartan

Like ACE inhibitors they should be used with caution in patients with renovascular disease. Side-effects include hypotension and hyperkalaemia.

Mechanism
- block effects of angiotensin II at the AT1 receptor

Evidence base
- shown to reduce progression of renal disease in patients with diabetic nephropathy
- evidence base that losartan reduces CVA and IHD mortality in hypertensive patients

## CENTRALLY ACTING ANTIHYPERTENSIVES

Examples of centrally acting antihypertensives include:
- methyldopa: used in the management of hypertension during pregnancy
- moxonidine: used in the management of essential hypertension when conventional antihypertensives have failed to control blood pressure
- clonidine: the antihypertensive effect is mediated through stimulating alpha-2 adrenoceptors in the vasomotor centre

## THIAZIDE DIURETICS

Thiazide diuretics work by inhibiting sodium reabsorption at the beginning of the distal convoluted tubule (DCT) by blocking the thiazide-sensitive $Na^+$-$Cl^-$ symporter. Potassium is lost as a result of more sodium reaching the collecting ducts. Thiazide diuretics have a role in the treatment of mild heart failure although loop diuretics are better for reducing overload. The main use of bendroflumethiazide was in the management of hypertension but recent NICE guidelines now recommend other thiazide-like diuretics such as indapamide and chlortalidone.

Common adverse effects
- dehydration
- postural hypotension
- hyponatraemia, hypokalaemia, hypercalcaemia*
- gout

- impaired glucose tolerance
- impotence

Rare adverse effects
- thrombocytopaenia
- agranulocytosis
- photosensitivity rash
- pancreatitis

*the flip side of this is hypocalciuria, which may be useful in reducing the incidence of renal stones

## LOOP DIURETICS

Furosemide and bumetanide are loop diuretics that act by inhibiting the Na-K-Cl cotransporter (NKCC) in the thick ascending limb of the loop of Henle, reducing the absorption of NaCl. There are two variants of NKCC; loop diuretics act on NKCC2, which is more prevalent in the kidneys.

Indications
- heart failure: both acute (usually intravenously) and chronic (usually orally)
- resistant hypertension, particularly in patients with renal impairment

Adverse effects
- hypotension
- hyponatraemia
- hypokalaemia, hypomagnesaemia
- hypochloraemic alkalosis
- ototoxicity
- hypocalcaemia
- renal impairment (from dehydration + direct toxic effect)
- hyperglycaemia (less common than with thiazides)
- gout

# BETA-BLOCKERS

Beta-blockers are an important class of drug used mainly in the management of cardiovascular disorders.

Indications
- angina
- post-myocardial infarction
- heart failure: beta-blockers were previously avoided in heart failure but there is now strong evidence that certain beta-blockers improve both symptoms and mortality
- arrhythmias: beta-blockers have now replaced digoxin as the rate-control drug of choice in atrial fibrillation
- hypertension: the role of beta-blockers has diminished in recent years due to a lack of evidence in terms of reducing stroke and myocardial infarction.
- thyrotoxicosis
- migraine prophylaxis
- anxiety

Examples
- atenolol
- propranolol: one of the first beta-blockers to be developed. Lipid soluble therefore crosses the blood-brain barrier

Side-effects
- bronchospasm
- cold peripheries
- fatigue
- sleep disturbances, including nightmares
- erectile dysfunction

Contraindications
- uncontrolled heart failure
- asthma
- sick sinus syndrome
- concurrent verapamil use: may precipitate severe bradycardia

# HYDRALAZINE

Hydralazine is one of the 'older' antihypertensives and is not commonly used nowadays. It is still sometimes used for hypertension in pregnancy and for severe hypertension.

Mechanism of action
- increases cGMP leading to smooth muscle relaxation

Contraindications
- systemic lupus erythematous
- ischaemic heart disease/cerebrovascular disease

Adverse effects
- tachycardia
- palpitations
- flushing
- fluid retention
- headache
- drug-induced lupus

# MALIGNANT HYPERTENSION

Basics
- severe hypertension (e.g. >200/130 mmHg)
- occurs in both essential and secondary types
- fibrinoid necrosis of blood vessels, leading to retinal haemorrhages, exudates, and proteinuria, haematuria due to renal damage (benign nephrosclerosis).
- can lead to cerebral oedema → encephalopathy

Features
- classically: severe headaches, nausea/vomiting, visual disturbance
- however chest pain and dyspnoea common presenting symptoms
- papilloedema
- severe: encephalopathy (e.g. seizures)

Management

- reduce diastolic no lower than 100mmHg within 12-24 hrs
- bed rest
- most patients: oral therapy e.g. atenolol
- if severe/encephalopathic: IV sodium nitroprusside/labetolol

## DIABETES MELLITUS: HYPERTENSION MANAGEMENT

Patient diabetes mellitus have traditionally had their blood pressure controlled more aggressively to help reduce their overall cardiovascular risk. However, a 2013 Cochrane review casted doubt on the wisdom of lower blood pressure targets for patients with diabetes. It compared patients who had tight blood pressure control (targets < 130/85 mmHg) with more relaxed control (< 140-160/90-100 mmHg). Patients who were more tightly controlled had a slightly reduced rate of stroke but otherwise outcomes were not significantly different.

In light of this, NICE recommends a blood pressure target of < 140/90 mmHg for type 2 diabetics, the same as for patients without diabetes.

For patients with type 1 diabetes, NICE recommends:

*Intervention levels for recommending blood pressure management should be 135/85 mmHg unless the adult with type 1 diabetes has albuminuria or 2 or more features of metabolic syndrome, in which case it should be 130/80 mmHg*

Because ACE-inhibitors have a renoprotective effect in diabetes they are the first-line antihypertensives recommended for NICE. Patients of African or Caribbean family origin should be offered an ACE-inhibitor plus either a thiazide diuretic or calcium channel blocker. Further management then reverts to that of non-diabetic patients, as discussed earlier in the module.

Remember than autonomic neuropathy may result in more postural symptoms in patients taking antihypertensive therapy.

The routine use of beta-blockers in uncomplicated hypertension should be avoided, particularly when given in combination with thiazides, as they may cause insulin resistance, impair insulin secretion and alter the autonomic response to hypoglycaemia.

# HYPERTENSION IN PREGNANCY

NICE published guidance in 2010 on the management of hypertension in pregnancy. They also made recommendations on reducing the risk of hypertensive disorders developing in the first place. Women who are at high risk of developing pre-eclampsia should take aspirin 75mg od from 12 weeks until the birth of the baby. High risk groups include:

- hypertensive disease during previous pregnancies
- chronic kidney disease
- autoimmune disorders such as SLE or antiphospholipid syndrome
- type 1 or 2 diabetes mellitus

The classification of hypertension in pregnancy is complicated and varies. Remember, in normal pregnancy:

- blood pressure usually falls in the first trimester (particularly the diastolic), and continues to fall until 20-24 weeks
- after this time the blood pressure usually increases to pre-pregnancy levels by term

Hypertension in pregnancy in usually defined as:

- systolic > 140 mmHg or diastolic > 90 mmHg
- or an increase above booking readings of > 30 mmHg systolic or > 15 mmHg diastolic

After establishing that the patient is hypertensive they should be categorised into one of the following groups

| Pre-existing hypertension | Pregnancy-induced hypertension (PIH, also known as gestational hypertension) | Pre-eclampsia |
|---|---|---|
| A history of hypertension before pregnancy or an elevated blood pressure > 140/90 mmHg before 20 weeks gestation | Hypertension (as defined above) occurring in the second half of pregnancy (i.e. after 20 weeks)<br>No proteinuria, no oedema | Pregnancy-induced hypertension in association with proteinuria (> 0.3g / 24 hours) |

| Pre-existing hypertension | Pregnancy-induced hypertension (PIH, also known as gestational hypertension) | Pre-eclampsia |
|---|---|---|
| No proteinuria, no oedema<br>Occurs in 3-5% of pregnancies and is more common in older women | Occurs in around 5-7% of pregnancies<br>Resolves following birth (typically after one month). Women with PIH are at increased risk of future pre-eclampsia or hypertension later in life | Oedema may occur but is now less commonly used as a criteria<br>Occurs in around 5% of pregnancies |

## ISOLATED SYSTOLIC HYPERTENSION

Isolated systolic hypertension (ISH) is common in the elderly, affecting around 50% of people older than 70 years old. The Systolic Hypertension in the Elderly Program (SHEP) back in 1991 established that treating ISH reduced both strokes and ischaemic heart disease. Drugs such as thiazides were recommended as first line agents. This approach is contradicted by the 2011 NICE guidelines which recommends treating ISH in the same stepwise fashion as standard hypertension.

## PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension (PAH) may be defined as a resting mean pulmonary artery pressure of >= 25 mmHg. Endothelin thought to play a key role in pathogenesis of PAH. It is more common in females and typically presents between the ages of 30-50 years. Pulmonary hypertension may of course develop secondary to chronic lung diseases such as COPD - PAH is diagnosed in the absence of this although certain factors increase the risk, including HIV, cocaine and anorexigens (e.g. fenfluramine). Around 10% of cases are inherited in an autosomal dominant fashion.

Features
- progressive exertional dyspnoea is the classical presentation
- other possible features include exertional syncope, exertional chest pain and peripheral oedema
- cyanosis

- right ventricular heave, loud P2, raised JVP with prominent 'a' waves, tricuspid regurgitation

Management should first involve treating any underlying conditions, for example with anticoagulants or oxygen. Following this, it has now been shown that acute vasodilator testing is central to deciding on the appropriate management strategy. Acute vasodilator testing aims to decide which patients show a significant fall in pulmonary arterial pressure following the administration of vasodilators such as intravenous epoprostenol or inhaled nitric oxide.

If there is a positive response to acute vasodilator testing (a minority of patients)

- oral calcium channel blockers

If there is a negative response to acute vasodilator testing (the vast majority of patients)

- prostacyclin analogues: treprostinil, iloprost
- endothelin receptor antagonists: bosentan, ambrisentan
- phosphodiesterase inhibitors: sildenafil

Patients with progressive symptoms should be considered for a heart-lung transplant.

# PULMONARY EMBOLISM: INVESTIGATION

We know from experience that few patients (around 10%) present with the medical student textbook triad of pleuritic chest pain, dyspnoea and haemoptysis. Pulmonary embolism can be difficult to diagnose as it can present with virtually any cardiorespiratory symptom/sign depending on its location and size.

**So which features make pulmonary embolism more likely?**
The PIOPED study1 in 2007 looked at the frequency of different symptoms and signs in patients who were diagnosed with pulmonary embolism.

The relative frequency of common clinical signs is shown below:
- Tachypnea (respiratory rate >20/min) - 96%
- Crackles - 58%
- Tachycardia (heart rate >100/min) - 44%
- Fever (temperature >37.8°C) - 43%

It is interesting to note that the Well's criteria for diagnosing a PE use tachycardia rather than tachypnoea.

**2020 NICE guidelines**
All patients with symptoms or signs suggestive of a PE should have a history taken, examination performed and a chest x-ray to exclude other pathology.

NICE updated their guidelines on the investigation and management of venous thromboembolism (VTE) in 2020. One of the key changes was the use of the pulmonary embolism rule-out criteria (the PERC rule)
- a link is provided to PERC rule in the external link section
- this should be done when you think there is a low probability of PE, but want more reassurance that it isn't the diagnosis

- NICE define this low probability as < 15%, although it is clearly difficult to quantify such judgements
- if your suspicion of PE is greater than this then you should move straight to the 2-level PE Wells score, without doing a PERC

If a PE is suspected a 2-level PE Wells score should be performed

| Clinical feature | Points |
|---|---|
| Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins) | 3 |
| An alternative diagnosis is less likely than PE | 3 |
| Heart rate > 100 beats per minute | 1.5 |
| Immobilisation for more than 3 days or surgery in the previous 4 weeks | 1.5 |
| Previous DVT/PE | 1.5 |
| Haemoptysis | 1 |
| Malignancy (on treatment, treated in the last 6 months, or palliative) | 1 |

Clinical probability simplified scores
- PE likely - more than 4 points
- PE unlikely - 4 points or less

If a PE is 'likely' (more than 4 points) arrange an immediate computed tomography pulmonary angiogram (CTPA). If there is a delay in getting the CTPA then interim therapeutic anticoagulation should be given until the scan is performed.
- interim therapeutic anticoagulation used to mean giving low-molecular weight heparin
- NICE updated their guidance in 2020. They now recommend using an anticoagulant that can be continued if the result is positive.
- this means normally a direct oral anticoagulant (DOAC) such as apixaban or rivaroxaban

If a PE is 'unlikely' (4 points or less) arranged a D-dimer test
- if positive arrange an immediate computed tomography pulmonary angiogram (CTPA)
  - if there is a delay in getting the CTPA then give interim therapeutic anticoagulation until the scan is performed
- if negative then PE is unlikely - consider an alternative diangosis

If the patient has an allergy to contrast media or renal impairment a V/Q scan should be used instead of a CTPA.

**CTPA or V/Q scan?**

The consensus view from the British Thoracic Society and NICE guidelines is as follows:

- CTPA is now the recommended initial lung-imaging modality for non-massive PE. Advantages compared to V/Q scans include speed, easier to perform out-of-hours, a reduced need for further imaging and the possibility of providing an alternative diagnosis if PE is excluded
- if the CTPA is negative then patients do not need further investigations or treatment for PE
- V/Q scanning may be used initially if appropriate facilities exist, the chest x-ray is normal, and there is no significant symptomatic concurrent cardiopulmonary disease. V/Q scanning is also the investigation of choice if there is renal impairment (doesn't require the use of contrast unlike CTPA)

**Some other points**

D-dimers
- sensitivity = 95-98%, but poor specificity

ECG
- the classic ECG changes seen in PE are a large S wave in lead I, a large Q wave in lead III and an inverted T wave in lead III - 'S1Q3T3'. However, this change is seen in no more than 20% of patients
- right bundle branch block and right axis deviation are also associated with PE
- sinus tachycardia may also be seen

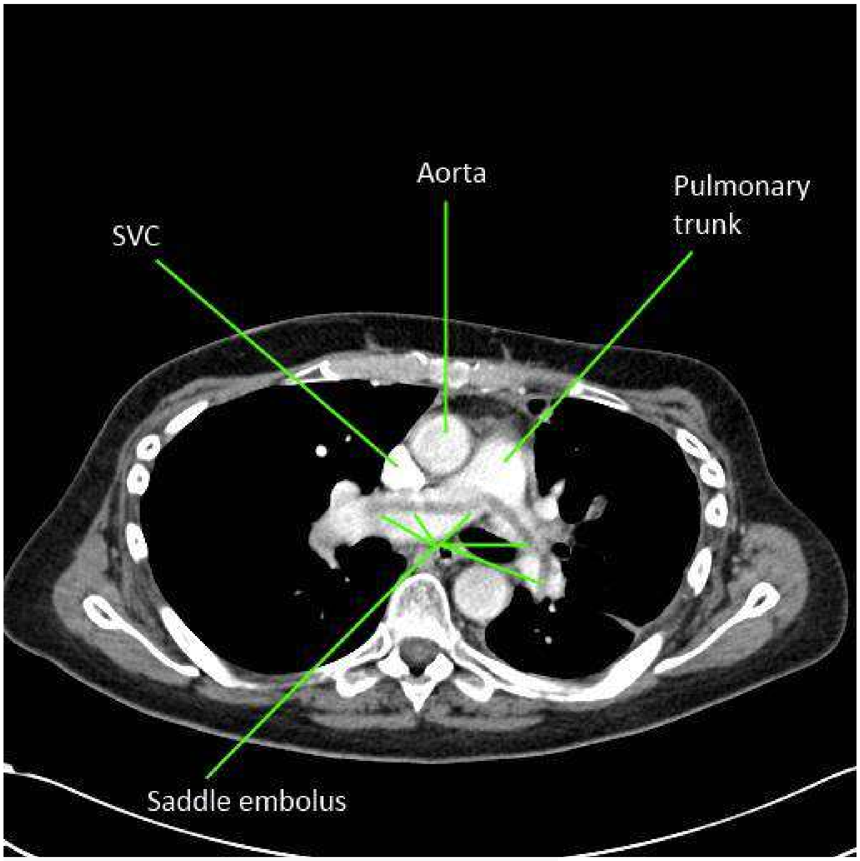
Chest x-ray
- a chest x-ray is recommended for all patients to exclude other pathology
- however, it is typically normal in PE
- possible findings include a wedge-shaped opacification

V/Q scan
- sensitivity of around 75% and specificity of 97%
- other causes of mismatch in V/Q include old pulmonary embolisms, AV malformations, vasculitis, previous radiotherapy
- COPD gives matched defects

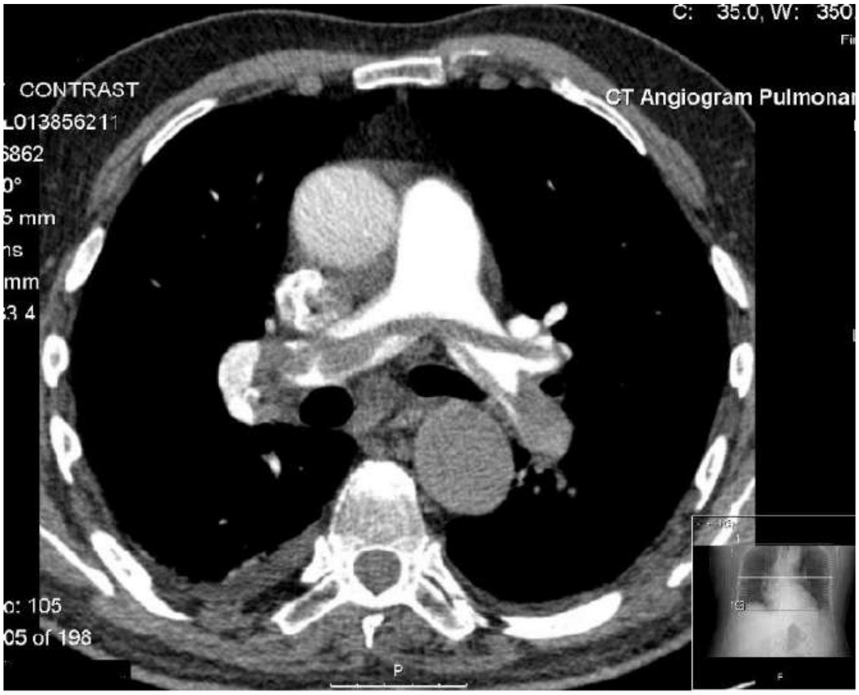
CTPA
- peripheral emboli affecting subsegmental arteries may be missed

Pulmonary angiography

- the gold standard
- significant complication rate compared to other investigations


Aorta
Pulmonary trunk
SVC
Saddle embolus

Labelled CTPA showing a large saddle embolus


C: 35.0, W: 350
CONTRAST
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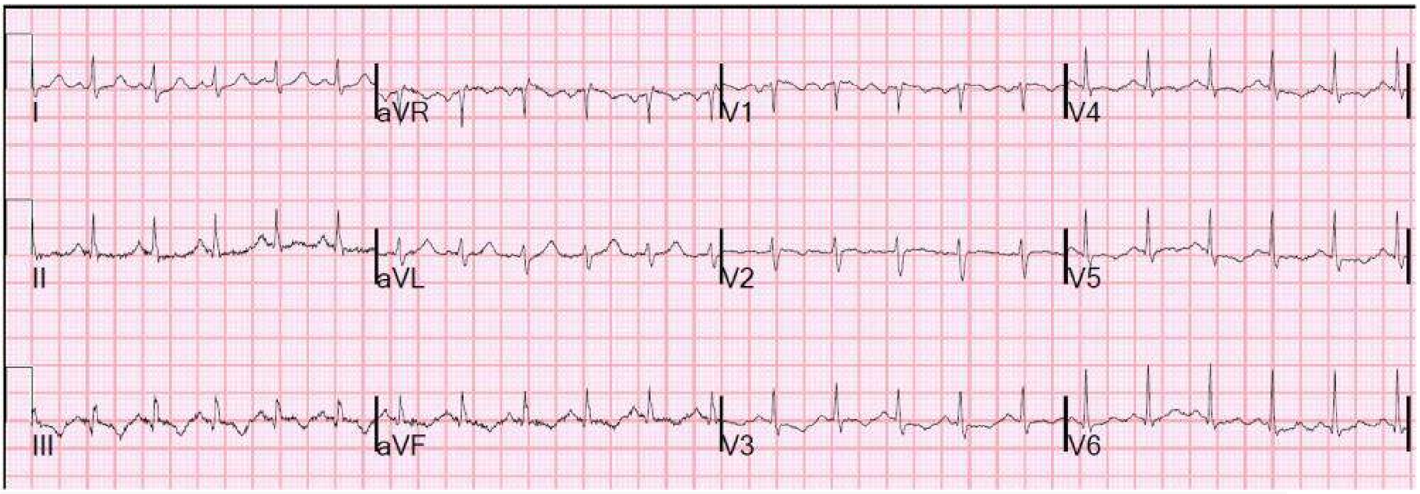
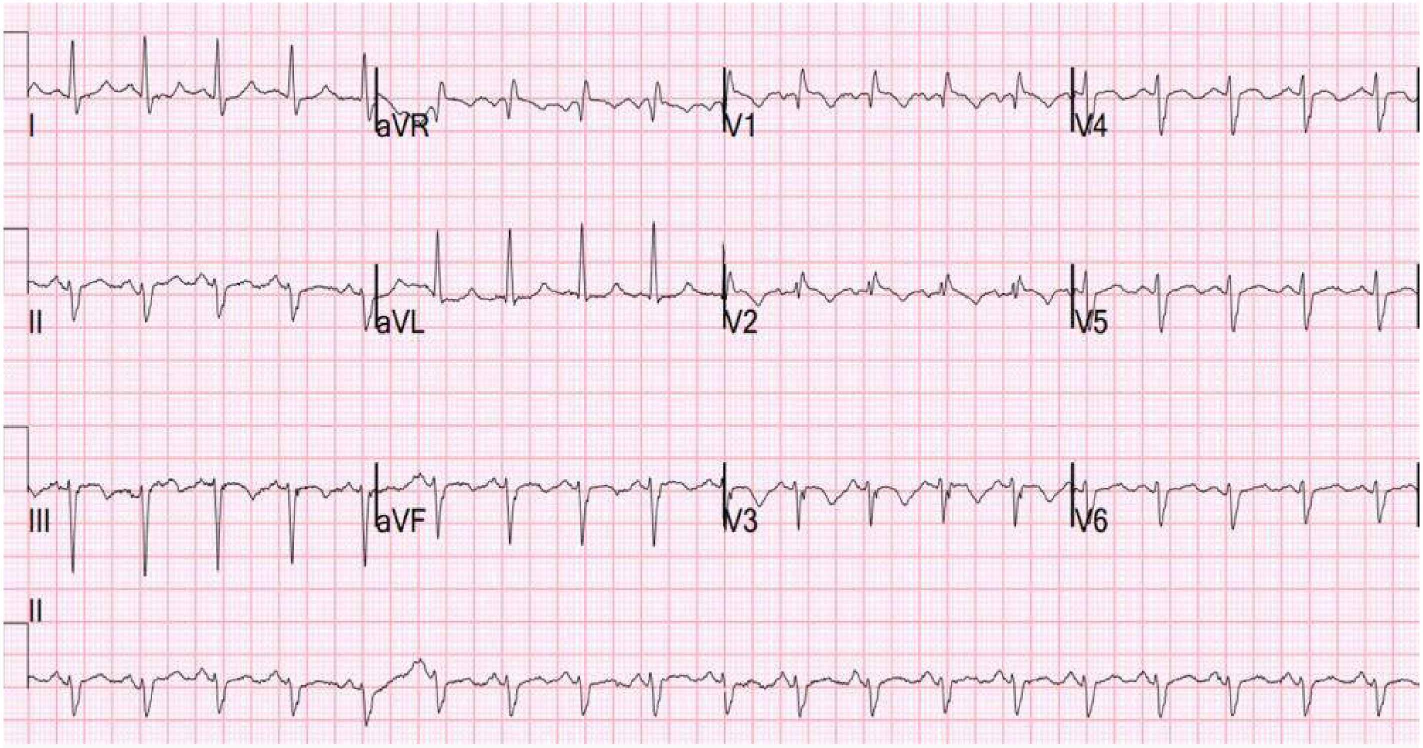
Further CTPA again showing a saddle embolus



ECG from a patient with a PE. Shows a sinus tachycardia and a partial S1Q3T3 - the S wave is not particularly convincing.



ECG of a patient with a PE. It shows some of the ECG features that may be associated with PE (sinus tachycardia, S1, T3 and T wave inversion in the precordial leads). Other features such as the left axis deviation are atypical.

1. Clinical Characteristics of Patients with Acute Pulmonary Embolism(Data from PIOPED II) Am J Med. Oct 2007; 120(10): 871879.

**Pulmonary embolism: management**

NICE updated their guidelines on the management of venous thromboembolism (VTE) in 2020. Some of the key changes include recommending the following:

- the use of direct oral anticoagulants (DOACs) as first-line treatment for most people with VTE

- the use of DOACs in patients with active cancer, as opposed to low-molecular weight heparin as was the previous recommendation
- outpatient treatment in low-risk pulmonary embolism (PE) patients
- routine cancer screening is no longer recommended following a VTE diagnosis

**Outpatient treatment in low-risk PE patients**
Deep vein thrombosis has for a long time been treated on an outpatient condition. In contrast, patients with any form of PE were typically admitted. However, in recent years patients with a new diagnosis of PE who are deemed low-risk are now increasingly managed as outpatients. NICE formally supported this approach in their latest guidance.

- NICE recommends using a 'validated risk stratification tool' to determine the suitability of outpatient treatment.
    - no guidance is given as to what tool should be used
    - the 2018 British Society guidelines support the use of the Pulmonary Embolism Severity Index (PESI) score
- key requirements would clearly be haemodynamic stability, lack of comorbidities and support at home

**Anticogulant therapy**
The cornerstone of VTE management is anticoagulant therapy. This was historically done with warfarin, often preceded by heparin until the INR was stable. However, the development of DOACs, and an evidence base supporting their efficacy, has changed modern management.

Choice of anticoagulant

- the big change in the 2020 guidelines was the increased use of DOACs
- apixaban or rivaroxaban (both DOACs) should be offered first-line following the diagnosis of a PE
    - instead of using low-molecular weight heparin (LMWH) until the diagnosis is confirmed, NICE now advocate using a DOAC once a diagnosis is suspected, with this continued if the diagnosis is confirmed
    - if neither apixaban or rivaroxaban are suitable then either LMWH followed by dabigatran or edoxaban OR LMWH followed by a vitamin K antagonist (VKA, i.e. warfarin)
- if the patient has active cancer
    - previously LMWH was recommended
    - the new guidelines now recommend using a DOAC, unless this is contraindicated

- if renal impairment is severe (e.g. < 15/min) then LMWH, unfractionated heparin or LMWH followed by a VKA
- if the patient has antiphospholipid syndrome (specifically 'triple positive' in the guidance) then LMWH followed by a VKA should be used

Length of anticoagulation

- all patients should have anticoagulation for at least 3 months
- continuing anticoagulation after this period is partly determined by whether the VTE was provoked or unprovoked
    - a provoked VTE is due to an obvious precipitating event e.g. immobilisation following major surgery. The implication is that this event was transient and the patient is no longer at increased risk
    - an unprovoked VTE occurs in the absence of an obvious precipitating event, i.e. there is a possibility that there are unknown factors (e.g. mild thrombophilia) making the patient more at risk from further clots
- if the VTE was provoked the treatment is typically stopped after the initial 3 months (3 to 6 months for people with active cancer)
- if the VTE was unprovoked then treatment is typically continued for up to 3 further months (i.e. 6 months in total)
    - NICE recommend that whether a patient has a total of 3-6 months anticoagulant is based upon balancing a person's risk of VTE recurrence and their risk of bleeding
    - the HAS-BLED score can be used to help assess the risk of bleeding
    - NICE state: 'Explain to people with unprovoked DVT or PE and a low bleeding risk that the benefits of continuing anticoagulation treatment are likely to outweigh the risks. '. The implication of this is that in the absence of a bleeding risk factors, patients are generally better off continuing anticoagulation for a total of 6 months

**PE with haemodynamic instability**

Thrombolysis

- thrombolysis is now recommended as the first-line treatment for massive PE where there is circulatory failure (e.g. hypotension)
- other invasive approaches should be considered where appropriate facilities exist

Patients who have repeat pulmonary embolisms, despite adequate anticoagulation, may be considered for inferior vena cava (IVC) filters. These work by stopping clots formed in the deep veins of the leg from moving to the pulmonary arteries. IVC filter use is currently supported by NICE but other studies suggest a weak evidence base - please see the link for more details.

# PREGNANCY: DVT/PE INVESTIGATION

Guidelines were updated in 2015 by the Royal College of Obstetricians.

For patients with a suspected deep vein thrombosis (DVT):

- Compression duplex ultrasound should be undertaken where there is clinical suspicion of DVT

For patients with a suspected pulmonary embolism (PE):

- ECG and chest x-ray should be performed in all patients
- In women who also have symptoms and signs of DVT, compression duplex ultrasound should be performed. If compression ultrasonography confirms the presence of DVT, no further investigation is necessary and treatment for VTE should continue
- the decision to perform a V/Q or CTPA should be taken at a local level after discussion with the patient and radiologist

**Comparing CTPA to V/Q scanning in pregnancy**

| CTPA | V/Q scanning |
|---|---|
| CTPA slightly increases the lifetime risk of **maternal breast cancer** (increased by up to 13.6%, background risk of 1/200 for study population). Pregnancy makes breast tissue particularly sensitive to the effects of radiation | V/Q scanning carries a slightly increased risk of **childhood cancer** compared with CTPA (1/50,000 versus less than 1/1,000,000) |

D-dimer is of limited use in the investigation of thromboembolism as it often raised in pregnancy.

# PARADOXICAL EMBOLISATION

For a right-sided thrombus (e.g. DVT) to cause a left-sided embolism (e.g. stroke) it must obviously pass from the right-to-left side of the heart

The following cardiac lesions may cause such events
- patent foramen ovale - present in around 20% of the population
- atrial septal defect - a much less common cause

## CHOLESTEROL EMBOLISATION

Overview
- cholesterol emboli may break off causing renal disease
- the majority of cases are secondary to vascular surgery or angiography. Other causes include severe atherosclerosis, particularly in large arteries such as the aorta

Features
- eosinophilia
- purpura
- renal failure
- livedo reticularis

# PERIPHERAL ARTERIAL DISEASE: MANAGEMENT

Peripheral arterial disease (PAD) is strongly linked to smoking. Patients who still smoke should be given help to quit smoking.

**Comorbidities should be treated**, including
- hypertension
- diabetes mellitus
- obesity

As with any patient who has established cardiovascular disease, all patients should be taking a statin. Atorvastatin 80 mg is currently recommended. In 2010 NICE published guidance suggesting that clopidogrel should be used first-line in patients with peripheral arterial disease in preference to aspirin.

**Exercise training** has been shown to have significant benefits. NICE recommend a supervised exercise programme for all patients with peripheral arterial disease prior to other interventions.

Severe PAD or critical limb ischaemia may be treated by:
- angioplasty
- stenting
- bypass surgery

Amputation should be reserved for patients with critical limb ischaemia who are not suitable for other interventions such as angioplasty of bypass surgery.

Drugs licensed for use in peripheral arterial disease (PAD) include:
- naftidrofuryl oxalate: vasodilator, sometimes used for patients with a poor quality of life
- cilostazol: phosphodiesterase III inhibitor with both antiplatelet and vasodilator effects - not recommended by NICE

# ATRIAL MYXOMA

Atrial myxoma is the most common primary cardiac tumour.

Overview
- 75% occur in left atrium, most commonly attached to the fossa ovalis
- more common in females

Features
- systemic: dyspnoea, fatigue, weight loss, pyrexia of unknown origin, clubbing
- emboli
- atrial fibrillation
- mid-diastolic murmur, 'tumour plop'
- echo: pedunculated heterogeneous mass typically attached to the fossa ovalis region of the interatrial septum

# SYNDROME X

Features
- angina-like chest pain on exertion
- ST depression on exercise stress test
- but normal coronary arteries on angiography

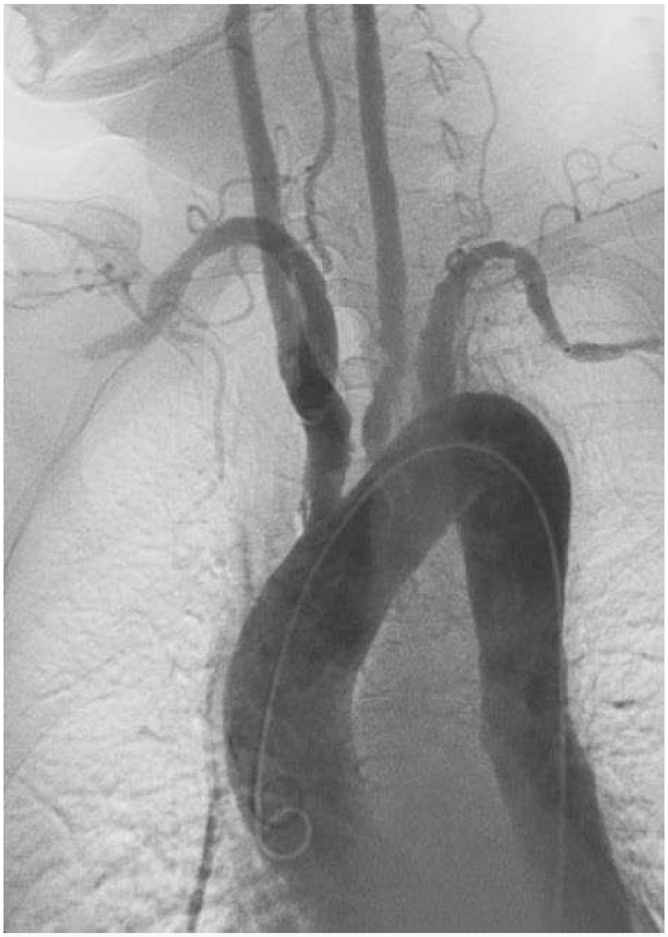
Management
- nitrates may be beneficial

# TAKAYASU'S ARTERITIS

Takayasu's arteritis is a large vessel vasculitis. It typically causes occlusion of the aorta and questions commonly refer to an absent limb pulse. It is more common in females and Asian people

Features
- systemic features of a vasculitis e.g. malaise, headache

- unequal blood pressure in the upper limbs
- carotid bruit
- intermittent claudication
- aortic regurgitation (around 20%)



Angiography showing multiple stenoses in the branches of the aorta secondary to Takayasu's arteritis

Associations

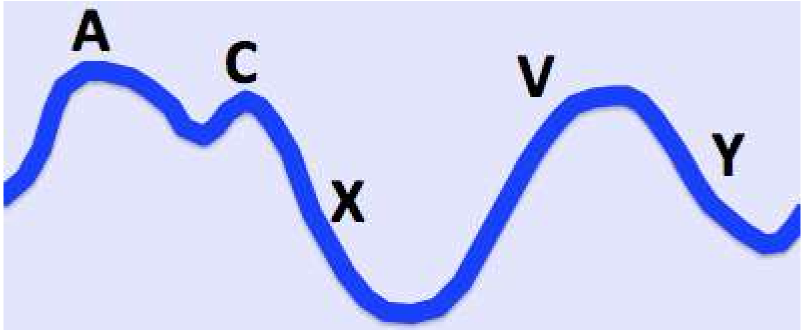
- renal artery stenosis

Management

- steroids

# JUGULAR VENOUS PULSE

As well as providing information on right atrial pressure, the jugular vein waveform may provide clues to underlying valvular disease. A non-pulsatile JVP is seen in superior vena caval obstruction. Kussmaul's sign describes a paradoxical rise in JVP during inspiration seen in constrictive pericarditis.



'a' wave = atrial contraction
- large if atrial pressure e.g. tricuspid stenosis, pulmonary stenosis, pulmonary hypertension
- absent if in atrial fibrillation

Cannon 'a' waves
- caused by atrial contractions against a closed tricuspid valve
- are seen in complete heart block, ventricular tachycardia/ectopics, nodal rhythm, single chamber ventricular pacing

'c' wave
- closure of tricuspid valve
- not normally visible

'v' wave
- due to passive filling of blood into the atrium against a closed tricuspid valve
- giant v waves in tricuspid regurgitation

'x' descent = fall in atrial pressure during ventricular systole

'y' descent = opening of tricuspid valve

# JVP: CANNON WAVES

Caused by the right atrium contracting against a closed tricuspid valve. May be subdivided into regular or intermittent

Regular cannon waves
- ventricular tachycardia (with 1:1 ventricular-atrial conduction)
- atrio-ventricular nodal re-entry tachycardia (AVNRT)

Irregular cannon waves
- complete heart block

# CARDIAC IMAGING: NON-INVASIVE TECHNIQUES EXCLUDING ECHOCARDIOGRAPHY

The ability to image the heart using non-invasive techniques such as MRI, CT and radionuclides has evolved rapidly over recent years.

**Nuclear imaging**

These techniques use radiotracers which are extracted by normal myocardium. Examples include:

- thallium
- technetium (99mTc) sestamibi: a coordination complex of the radioisotope technetium-99m with the ligand methoxyisobutyl isonitrile (MIBI), used in 'MIBI' or cardiac Single Photon Emission Computed Tomography (SPECT) scans
- fluorodeoxyglucose (FDG): used in Positron Emission Tomography (PET) scans

The primary role of SPECT is to assess myocardial perfusion and myocardial viability. Two sets of images are usually acquired. First the myocardium at rest followed by images of the myocardium during stress (either exercise or following adenosine / dipyridamole). By comparing the rest with stress images any areas of ischaemia can classified as reversible or fixed (e.g. Following a myocardial infarction). Cardiac PET is predominately a research tool at the current time

**MUGA**

- Multi Gated Acquisition Scan, also known as radionuclide angiography
- radionuclide (technetium-99m) is injected intravenously
- the patient is placed under a gamma camera
- may be performed as a stress test
- can accurately measure left ventricular ejection fraction. Typically used before and after cardiotoxic drugs are used

**Cardiac Computed Tomography (CT)**

Cardiac CT is useful for assessing suspected ischaemic heart disease, using two main methods:

- calcium score: there is known to be a correlation between the amount of atherosclerotic plaque calcium and the risk of future ischaemic events. Cardiac CT can quantify the amount of calcium producing a 'calcium score'
- contrast enhanced CT: allows visualisation of the coronary artery lumen

If these two techniques are combined cardiac CT has a very high negative predictive value for ischaemic heart disease.

**Cardiac MRI**

Cardiac MRI (commonly termed CMR) has become the gold standard for providing structural images of the heart. It is particularly useful when assessing congenital heart disease, determining right and left ventricular mass and differentiating forms of cardiomyopathy. Myocardial perfusion can also be assessed following the administration of gadolinium. Currently CMR provides limited data on the extent of coronary artery disease.

Please also see the British Heart Foundation link for an excellent summary.

# SCORING SYSTEMS

There are now numerous scoring systems used in medicine. The table below lists some of the more common ones:

| Scoring system | Notes |
|---|---|
| **$CHA_2DS_2$-VASc** | Used to determine the need to anticoagulate a patient in atrial fibrillation |
| **ABCD2** | Prognostic score for risk stratifying patients who've had a suspected TIA |
| **NYHA** | Heart failure severity scale |
| **DAS28** | Measure of disease activity in rheumatoid arthritis |
| **Child-Pugh classification** | A scoring system used to assess the severity of liver cirrhosis |
| **Wells score** | Helps estimate the risk of a patient having a deep vein thrombosis |
| **MMSE** | Mini-mental state examination - used to assess cognitive impairment |
| **HAD** | Hospital Anxiety and Depression (HAD) scale - assesses severity of anxiety and depression symptoms |
| **PHQ-9** | Patient Health Questionnaire - assesses severity of depression symptoms |
| **GAD-7** | Used as a screening tool and severity measure for generalised anxiety disorder |
| **Edinburgh Postnatal Depression Score** | Used to screen for postnatal depression |
| **SCOFF** | Questionnaire used to detect eating disorders and aid treatment |
| **AUDIT** | Alcohol screening tool |
| **CAGE** | Alcohol screening tool |
| **FAST*** | Alcohol screening tool |
| **CURB-65** | Used to assess the prognosis of a patient with pneumonia |
| **Epworth Sleepiness Scale** | Used in the assessment of suspected obstructive sleep apnoea |
| **IPSS** | International prostate symptom score |
| **Gleason score** | Indicates prognosis in prostate cancer |
| **APGAR** | Assesses the health of a newborn immediately after birth |
| **Bishop score** | Used to help assess the whether induction of labour will be required |
| **Waterlow score** | Assesses the risk of a patient developing a pressure sore |
| **FRAX** | Risk assessment tool developed by WHO which calculates a patients 10-year risk of developing an osteoporosis related fracture |
| **Ranson criteria** | Acute pancreatitis |
| **MUST** | Malnutrition |

*FAST is also mnemonic to help patients/relatives identify the symptoms of a stroke

# DVLA: CARDIOVASCULAR DISORDERS

The guidelines below relate to car/motorcycle use unless specifically stated. For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter

Specific rules

- hypertension - can drive unless treatment causes unacceptable side effects, no need to notify DVLA. If Group 2 Entitlement the disqualifies from driving if resting BP consistently 180 mmHg systolic or more and/or 100 mm Hg diastolic or more
- angioplasty (elective) - 1 week off driving
- CABG - 4 weeks off driving
- acute coronary syndrome- 4 weeks off driving, 1 week if successfully treated by angioplasty
- angina - driving must cease if symptoms occur at rest/at the wheel
- pacemaker insertion - 1 week off driving
- implantable cardioverter-defibrillator (ICD): if implanted for sustained ventricular arrhythmia: cease driving for 6 months. If implanted prophylatically then cease driving for 1 month. Having an ICD results in a permanent bar for Group 2 drivers
- successful catheter ablation for an arrhythmia- 2 days off driving
- aortic aneurysm of 6cm or more - notify DVLA. Licensing will be permitted subject to annual review. An aortic diameter of 6.5 cm or more disqualifies patients from driving
- heart transplant: DVLA do not need to be notified

# PASSMEDICINE NOTES

# RESPIRATORY MEDICINE

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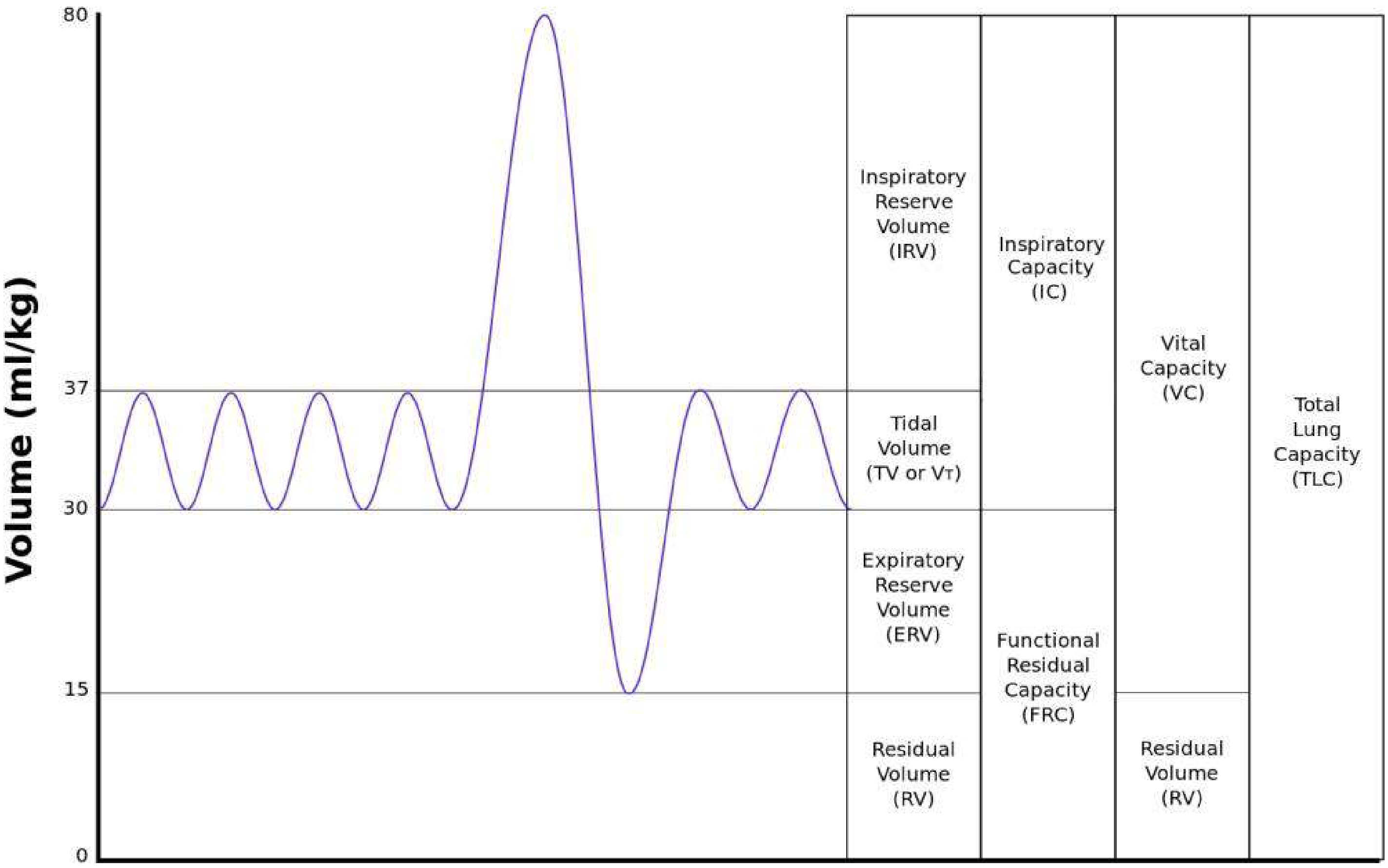
# RESPIRATORY PHYSIOLOGY: LUNG VOLUMES

The diagram below demonstrates the lung volumes which may be measured:



Tidal volume (TV)

- volume inspired or expired with each breath at rest
- 500ml in males, 350ml in females

Inspiratory reserve volume (IRV) = 2-3 L

- maximum volume of air that can be inspired at the end of a normal tidal inspiration
- inspiratory capacity = TV + IRV

Expiratory reserve volume (ERV) = 750ml

- maximum volume of air that can be expired at the end of a normal tidal expiration

Residual volume (RV) = 1.2L

- volume of air remaining after maximal expiration
- increases with age
- RV = FRC - ERV

Functional residual capacity (FRC)

- the volume in the lungs at the end-expiratory position
- FRC = ERV + RV

Vital capacity (VC) = 5L
- maximum volume of air that can be expired after a maximal inspiration
- 4,500ml in males, 3,500 mls in females
- decreases with age
- VC = inspiratory capacity + ERV

Total lung capacity (TLC) is the sum of the vital capacity + residual volume

Physiological dead space (VD)
- VD = tidal volume * ($PaCO_2$ - $PeCO_2$) / $PaCO_2$
- where $PeCO_2$ = expired air $CO_2$

# TRANSFER FACTOR

The transfer factor describes the rate at which a gas will diffuse from alveoli into blood. Carbon monoxide is used to test the rate of diffusion. Results may be given as the total gas transfer (TLCO) or that corrected for lung volume (transfer coefficient, KCO)

| **Causes of a raised TLCO** | **Causes of a lower TLCO** |
|---|---|
| **asthma**<br>**pulmonary haemorrhage (Wegener's, Goodpasture's)**<br>**left-to-right cardiac shunts**<br>**polycythaemia**<br>**hyperkinetic states**<br>**male gender, exercise** | **pulmonary fibrosis**<br>**pneumonia**<br>**pulmonary emboli**<br>**pulmonary oedema**<br>**emphysema**<br>**anaemia**<br>**low cardiac output** |

KCO also tends to increase with age. Some conditions may cause an increased KCO with a normal or reduced TLCO
- pneumonectomy/lobectomy
- scoliosis/kyphosis
- neuromuscular weakness
- ankylosis of costovertebral joints e.g. ankylosing spondylitis

# OXYGEN DISSOCIATION CURVE

The oxygen dissociation curve describes the relationship between the percentage of saturated haemoglobin and partial pressure of oxygen in the blood. It is not affected by haemoglobin concentration

Basics

- shifts to left = for given oxygen tension there is increased saturation of Hb with oxygen i.e. decreased oxygen delivery to tissues
- shifts to right = for given oxygen tension there is reduced saturation of Hb with oxygen i.e. enhanced oxygen delivery to tissues
-

| Shifts to Left = Lower oxygen delivery | Shifts to Right = Raised oxygen delivery |
|---|---|
| HbF, methaemoglobin, carboxyhaemoglobin<br>Low [H+] (alkali)<br>Low pCO2<br>Low 2,3-DPG<br>Low temperature | Raised [H+] (acidic)<br>Raised pCO2<br>Raised 2,3-DPG*<br>Raised temperature |

The **L** rule

Shifts to **L** → **L**ower oxygen delivery, caused by

- **L**ow [H+] (alkali)
- **L**ow pCO2
- **L**ow 2,3-DPG
- **L**ow temperature

Another mnemonic is '**CADET**, face Right!' for **C**O2, **A**cid, 2,3-**D**PG, **E**xercise and **T**emperature

*2,3-diphosphoglycerate

# PULMONARY FUNCTION TESTS

Pulmonary function tests can be used to determine whether a respiratory disease is obstructive or restrictive. The table below summarises the main findings and gives some example conditions:

| Obstructive lung disease | Restrictive lung disease |
|---|---|
| FEV1 - significantly reduced<br>FVC - reduced or normal<br>FEV1% (FEV1/FVC) - reduced | FEV1 - reduced<br>FVC - significantly reduced<br>FEV1% (FEV1/FVC) - normal or increased |
| Asthma<br>COPD<br>Bronchiectasis<br>Bronchiolitis obliterans | Pulmonary fibrosis<br>Asbestosis<br>Sarcoidosis<br>Acute respiratory distress syndrome<br>Infant respiratory distress syndrome<br>Kyphoscoliosis e.g. ankylosing spondylitis<br>Neuromuscular disorders<br>Severe obesity |

# FLOW VOLUME LOOP

A normal flow volume loop is often described as a 'triangle on top of a semi circle'

Flow volume loops are the most suitable way of assessing compression of the upper airway

# RESPIRATORY ACIDOSIS

Respiratory acidosis may be caused by a number of conditions:
- COPD
- decompensation in other respiratory conditions e.g. life-threatening asthma / pulmonary oedema
- neuromuscular disease
- obesity hypoventilation syndrome
- sedative drugs: benzodiazepines, opiate overdose

# RESPIRATORY ALKALOSIS

Common causes
- anxiety leading to hyperventilation
- pulmonary embolism
- salicylate poisoning*
- CNS disorders: stroke, subarachnoid haemorrhage, encephalitis
- altitude

- pregnancy

*salicylate overdose leads to a mixed respiratory alkalosis and metabolic acidosis. Early stimulation of the respiratory centre leads to a respiratory alkalosis whilst later the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis

## CHEST X-RAY: CAVITATING LUNG LESION

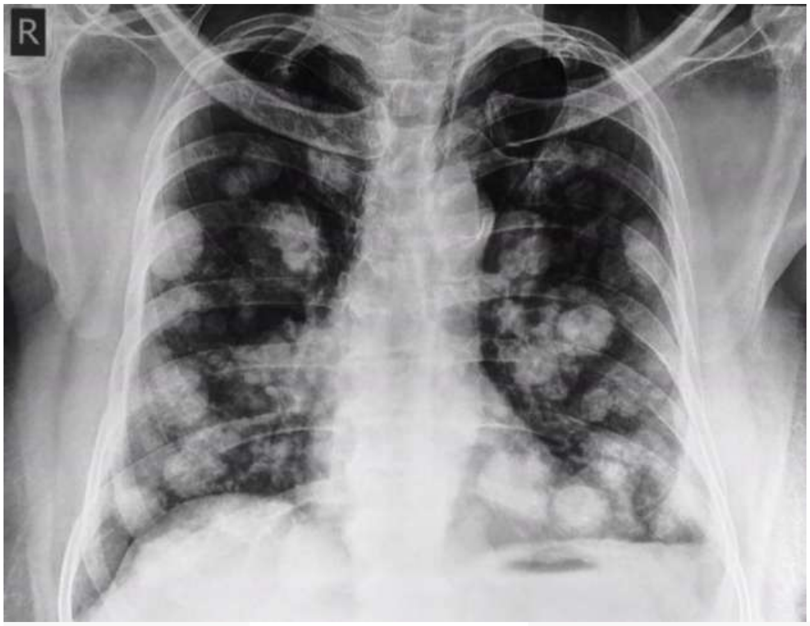
Differential
- abscess (Staph aureus, Klebsiella and Pseudomonas)
- squamous cell lung cancer
- tuberculosis
- Wegener's granulomatosis
- pulmonary embolism
- rheumatoid arthritis
- aspergillosis, histoplasmosis, coccidioidomycosis

## CHEST X-RAY: LUNG METASTASES

Lung metastases are seen with a wide variety of cancers including:
- breast cancer
- colorectal cancer
- renal cell cancer
- bladder cancer
- prostate cancer

Multiple, round well-defined lung secondaries are often referred to as 'cannonball metastases'. They are most commonly seen with renal cell cancer but may also occur secondary to choriocarcinoma and prostate cancer.

Calcification in lung metastases is uncommon except in the case of chondrosarcoma or osteosarcoma.



Chest x-ray showing **cannonball metastases** secondary to renal cell cancer. Multiple well defined nodules are noted distributed in both lung fields

# ASTHMA: DIAGNOSIS

NICE released guidance on the management of asthma in 2017. These followed on quickly from the 2016 British Thoracic Society (BTS) guidelines. Given previous precedents where specialist societies or Royal colleges eventually default/contribute to NICE, we have followed the NICE guidance for the notes and questions.

NICE guidance has radically changed how asthma should be diagnosed. It advocates moving anyway from subjective/clinical judgements are more towards **objective** tests.

There is particular emphasis on the use of **fractional exhaled nitric oxide (FeNO)**. Nitric oxide is produced by 3 types of nitric oxide synthases (NOS). One of the types is inducible (iNOS) and levels tend to rise in inflammatory cells, particularly eosinophils. Levels of NO therefore typically correlate with levels of inflammation.

Other more established objective tests such as spirometry and peak flow variability are still important.

All patients >= 5 years should have objective tests. Once a child with suspected asthma reaches the age of 5 years objective tests should be performed to confirm the diagnosis.

**Diagnostic testing**

Patients >= 17 years

- patients should be asked if their symptoms are better on days away from work/during holidays. If so, patients should be referred to a specialist as possible occupational asthma
- all patients should have spirometry with a bronchodilator reversibility (BDR) test
- all patients should have a FeNO test

Patients 5-16 years

- all patients should have spirometry with a bronchodilator reversibility (BDR) test
- a FeNO test should be requested if there is normal spirometry or obstructive spirometry with a negative bronchodilator reversibility (BDR) test

Patients < 5 years

- diagnosis should be made on clinical judgement

**Specific points about the tests**

FeNO

- in adults level of >= 40 parts per billion (ppb) is considered positive
- in children a level of >= 35 parts per billion (ppb) is considered positive

Spirometry

- FEV1/FVC ratio less than 70% (or below the lower limit of normal if this value is available) is considered obstructive

Reversibility testing

- in adults, a positive test is indicated by an improvement in FEV1 of 12% or more and increase in volume of 200 ml or more
- in children, a positive test is indicated by an improvement in FEV1 of 12% or more

# ASTHMA: MANAGEMENT IN ADULTS

NICE released guidance on the management of asthma in 2017. These followed on quickly from the 2016 British Thoracic Society (BTS) guidelines. Given previous precedents where specialist societies or Royal colleges eventually default/contribute to NICE, we have followed the NICE guidance for the notes and questions.

One of the key changes is in 'step 3' - patients on a SABA + ICS whose asthma is not well controlled should be offered a leukotriene receptor antagonist, not a LABA

NICE do not follow the stepwise approach of the previous BTS guidelines. However, to try to make the guidelines easier to follow we've added our own steps:

| Step | Notes |
|---|---|
| **1**<br>Newly-diagnosed asthma | Short-acting beta agonist (SABA) |
| **2**<br>Not controlled on previous step<br>OR<br>Newly-diagnosed asthma with symptoms >= 3 / week or night-time waking | SABA + low-dose inhaled corticosteroid (ICS) |
| **3** | SABA + low-dose ICS + leukotriene receptor antagonist (LTRA) |
| **4** | SABA + low-dose ICS + long-acting beta agonist (LABA)<br>Continue LTRA depending on patient's response to LTRA |
| **5** | SABA +/- LTRA<br>Switch ICS/LABA for a maintenance and reliever therapy (MART), that includes a low-dose ICS |
| **6** | SABA +/- LTRA + medium-dose ICS MART |

| Step | Notes |
|---|---|
| | OR consider changing back to a fixed-dose of a moderate-dose ICS and a separate LABA |
| **7** | SABA +/- LTRA + one of the following options:<br>• increase ICS to high-dose (only as part of a fixed-dose regime, not as a MART)<br>• a trial of an additional drug (for example, a long-acting muscarinic receptor antagonist or theophylline)<br>• seeking advice from a healthcare professional with expertise in asthma |

Maintenance and reliever therapy (MART)

- a form of combined ICS and LABA treatment in which a single inhaler, containing both ICS and a fast-acting LABA, is used for both daily maintenance therapy and the relief of symptoms as required
- MART is only available for ICS and LABA combinations in which the LABA has a fast-acting component (for example, formoterol)

It should be noted that NICE does not advocate changing treatment in patients who have well-controlled asthma simply to adhere to the latest guidance.

Table showing examples of inhaled corticosteroid doses

Frustratingly, the definitions of what constitutes a low, moderate or high-dose ICS have also changed. For adults:

- <= 400 micrograms budesonide or equivalent = low dose
- 400 micrograms - 800 micrograms budesonide or equivalent = moderate dose
- > 800 micrograms budesonide or equivalent= high dose.

# ACUTE ASTHMA: FEATURES

Acute asthma is nearly always seen in patients who've got a history of asthma.

Features

- worsening dyspnoea, wheeze and cough that is not responding to salbutamol
- maybe triggered by a respiratory tract infection

Patients with acute severe asthma are stratified into moderate, severe or life-threatening

| Moderate | Severe | Life-threatening |
|---|---|---|
| PEFR 50-75% best or predicted<br>Speech normal<br>RR < 25 / min<br>Pulse < 110 bpm | PEFR 33 - 50% best or predicted<br>Can't complete sentences<br>RR > 25/min<br>Pulse > 110 bpm | PEFR < 33% best or predicted<br>Oxygen sats < 92%<br>Silent chest, cyanosis or feeble respiratory effort<br>Bradycardia, dysrhythmia or hypotension<br>Exhaustion, confusion or coma |

In addition, a normal pCO2 in an acute asthma attack indicates exhaustion and should, therefore, be classified as life-threatening.

Note that a patient having any one of the life-threatening features should be treated as having a life-threatening attack.

British Thoracic Society guidelines
- magnesium sulphate recommended as next step for patients who are not responding (e.g. 1.2 - 2g IV over 20 mins)
- little evidence to support use of IV aminophylline (although still mentioned in management plans)
- if no response consider IV salbutamol

# ASTHMA: OCCUPATIONAL

Patients may either present with concerns that chemicals at work are worsening their asthma or you may notice in the history that symptoms seem better at weekends / when away from work.

Exposure to the following chemicals is associated with occupational asthma:
- isocyanates - the most common cause. Example occupations include spray painting and foam moulding using adhesives
- platinum salts
- soldering flux resin
- glutaraldehyde
- flour
- epoxy resins
- proteolytic enzymes

Serial measurements of peak expiratory flow are recommended at work and away from work.

Referral should be made to a respiratory specialist for patients with suspected occupational asthma.

# LEUKOTRIENE RECEPTOR ANTAGONISTS

Basics

- e.g. Montelukast, zafirlukast
- have both anti-inflammatory and bronchodilatory properties
- should be used when patients are poorly controlled on high-dose inhaled corticosteroids and a long-acting b2-agonist
- particularly useful in aspirin-induced asthma
- associated with the development of Churg-Strauss syndrome

# OMALIZUMAB

Omalizumab is a new drug that is available for the management of severe asthma. As it's name suggests it's a monoclonal antibody that specifically binds to free human immunoglobulin E (IgE).

Omalizumab is given as a subcutaneous injection every 2 to 4 weeks.

**Where does omalizumab fit into current management?**
NICE updated their technology appraisal of omalizumab in 2013. A copy of the criteria is given below. The emphasis in bold has been added.

*Omalizumab is recommended as an option for treating* ***severe persistent confirmed allergic IgE-mediated asthma as an add on to optimised standard therapy*** *in people aged 6 years and older:*

- *who need continuous or frequent treatment with* ***oral corticosteroids (defined as 4 or more courses in the previous year)***

*Optimised standard therapy is defined as a full trial of and, if tolerated, documented compliance with inhaled high-dose corticosteroids, long-acting beta agonists, leukotriene receptor antagonists, theophyllines, oral corticosteroids, and smoking cessation if clinically appropriate.*

Adverse effects

- abdominal pain
- headache
- fever
- Churg-Strauss syndrome: may present with eosinophilia, vasculitic rash, worsening respiratory symptoms and peripheral neuropathy

# COPD: CAUSES

Smoking!

Alpha-1 antitrypsin deficiency

Other causes
- cadmium (used in smelting)
- coal
- cotton
- cement
- grain

# COPD: INVESTIGATION AND DIAGNOSIS

NICE recommend considering a diagnosis of COPD in patients over 35 years of age who are smokers or ex-smokers and have symptoms such as exertional breathlessness, chronic cough or regular sputum production.

The following investigations are recommended in patients with suspected COPD:
- post-bronchodilator spirometry to demonstrate airflow obstruction: FEV1/FVC ratio less than 70%
- chest x-ray: hyperinflation, bullae, flat hemidiaphragm. Also important to exclude lung cancer
- full blood count: exclude secondary polycythaemia
- body mass index (BMI) calculation

The severity of COPD is categorised using the FEV1*:

| **Post-bronchodilator FEV1/FVC** | **FEV1 (of predicted)** | **Severity** |
|---|---|---|
| < 0.7 | > 80% | Stage 1 - Mild** |
| < 0.7 | 50-79% | Stage 2 - Moderate |
| < 0.7 | 30-49% | Stage 3 - Severe |
| < 0.7 | < 30% | Stage 4 - Very severe |

Measuring peak expiratory flow is of limited value in COPD, as it may underestimate the degree of airflow obstruction.

*note that the grading system has changed following the 2010 NICE guidelines. If the FEV1 is greater than 80% predicted but the post-bronchodilator FEV1/FVC is < 0.7 then this is classified as Stage 1 - mild

**symptoms should be present to diagnose COPD in these patients

# ACUTE EXACERBATION OF COPD

Acute exacerbations of COPD are one of the most common reasons why people present to hospital in developed countries.

Features
- increase in dyspnoea, cough, wheeze
- there may be an increase in sputum suggestive of an infective cause
- patients may be hypoxic and in some cases have acute confusion

The most common bacterial organisms that cause infective exacerbations of COPD are:
- Haemophilus influenzae (most common cause)
- Streptococcus pneumoniae
- Moraxella catarrhalis

Respiratory viruses account for around 30% of exacerbations, with the human rhinovirus being the most important pathogen.

NICE guidelines from 2010 recommend the following:
- increase frequency of bronchodilator use and consider giving via a nebuliser
- give prednisolone 30 mg daily for 7-14 days
- it is common practice for all patients with an exacerbation of COPD to receive antibiotics. NICE do not support this approach. They recommend giving oral antibiotics 'if sputum is purulent or there are clinical signs of pneumonia'
- the BNF recommends one of the following oral antibiotics first-line: amoxicillin or clarithromycin or doxycycline.

# COPD: STABLE MANAGEMENT

NICE updated its guidelines on the management of chronic obstructive pulmonary disease (COPD) in 2018.

General management
- > smoking cessation advice: including offering nicotine replacement therapy, varenicline or bupropion
- annual influenza vaccination
- one-off pneumococcal vaccination
- pulmonary rehabilitation to all people who view themselves as functionally disabled by COPD (usually Medical Research Council [MRC] grade 3 and above)

Bronchodilator therapy

- a short-acting beta2-agonist (SABA) or short-acting muscarinic antagonist (SAMA) is first-line treatment
- for patients who remain breathless or have exacerbations despite using short-acting bronchodilators the next step is determined by whether the patient has 'asthmatic features/features suggesting steroid responsiveness'

There are a number of criteria NICE suggest to determine whether a patient has asthmatic/steroid responsive features:

- any previous, secure diagnosis of asthma or of atopy
- a higher blood eosinophil count - note that NICE recommend a full blood count for all patients as part of the work-up
- substantial variation in FEV1 over time (at least 400 ml)
- substantial diurnal variation in peak expiratory flow (at least 20%)

Interestingly NICE do not recommend formal reversibility testing as one of the criteria. In the guidelines they state that 'routine spirometric reversibility testing is not necessary as part of the diagnostic process or to plan initial therapy with bronchodilators or corticosteroids. It may be unhelpful or misleading...'. They then go on to discuss why they have reached this conclusion. Please see the guidelines for more details.

No asthmatic features/features suggesting steroid responsiveness

- add a long-acting beta2-agonist (LABA) + long-acting muscarinic antagonist (LAMA)
    - if already taking a SAMA, discontinue and switch to a SABA

Asthmatic features/features suggesting steroid responsiveness

- LABA + inhaled corticosteroid (ICS)
- if patients remain breathless or have exacerbations offer triple therapy i.e. LAMA + LABA + ICS
    - if already taking a SAMA, discontinue and switch to a SABA
- NICE recommend the use of combined inhalers where possible

Oral theophylline

- NICE only recommends theophylline after trials of short and long-acting bronchodilators or to people who cannot used inhaled therapy
- the dose should be reduced if macrolide or fluoroquinolone antibiotics are co-prescribed

Oral prophylactic antibiotic therapy

- azithromycin prophylaxis is recommended in select patients
- patients should not smoke, have optimised standard treatments and continue to have exacerbations
- other prerequisites include a CT thorax (to exclude bronchiectasis) and sputum culture (to exclude atypical infections and tuberculosis)

- LFTs and an ECG to exclude QT prolongation should also be done as azithromycin can prolong the QT interval

Mucolytics
- should be 'considered' in patients with a chronic productive cough and continued if symptoms improve

Cor pulmonale
- features include peripheral oedema, raised jugular venous pressure, systolic parasternal heave, loud P2
- use a loop diuretic for oedema, consider long-term oxygen therapy
- ACE-inhibitors, calcium channel blockers and alpha blockers are not recommended by NICE

Factors which may improve survival in patients with stable COPD
- smoking cessation - the single most important intervention in patients who are still smoking
- long term oxygen therapy in patients who fit criteria
- lung volume reduction surgery in selected patients

# COPD: LONG-TERM OXYGEN THERAPY

The 2018 NICE guidelines on COPD clearly define which patients should be assessed for and offered long-term oxygen therapy (LTOT). Patients who receive LTOT should breathe supplementary oxygen for at least 15 hours a day. Oxygen concentrators are used to provide a fixed supply for LTOT.

Assess patients if any of the following:
- very severe airflow obstruction (FEV1 < 30% predicted). Assessment should be 'considered' for patients with severe airflow obstruction (FEV1 30-49% predicted)
- cyanosis
- polycythaemia
- peripheral oedema
- raised jugular venous pressure
- oxygen saturations less than or equal to 92% on room air

Assessment is done by measuring arterial blood gases on 2 occasions at least 3 weeks apart in patients with stable COPD on optimal management.

Offer LTOT to patients with a pO2 of < 7.3 kPa or to those with a pO2 of 7.3 - 8 kPa and one of the following:
- secondary polycythaemia
- peripheral oedema
- pulmonary hypertension

In terms of smoking, NICE advise the following:
- do not offer LTOT to people who continue to smoke despite being offered smoking cessation advice and treatment, and referral to specialist stop smoking services.

NICE suggest that a structured risk assessment is carried out before offering LTOT, including:
- the risks of falls from tripping over the equipment
- the risks of burns and fires, and the increased risk of these for people who live in homes where someone smokes (including e-cigarettes)

## OXYGEN THERAPY

The British Thoracic Society updated its guidelines on emergency oxygen therapy in 2017. The following selected points are taken from the guidelines. Please see the link provided for the full guideline.

In patients who are critically ill (anaphylaxis, shock etc) oxygen should initially be given via a reservoir mask at 15 l/min. Hypoxia kills. The BTS guidelines specifically exclude certain conditions where the patient is acutely unwell (e.g. myocardial infarction) but stable.

Oxygen saturation targets
- acutely ill patients: 94-98%
- patients at risk of hypercapnia (e.g. COPD patients): 88-92% (see below)
- oxygen should be reduced in stable patients with satisfactory oxygen saturation

Management of COPD patients
- prior to availability of blood gases, use a 28% Venturi mask at 4 l/min and aim for an oxygen saturation of 88-92% for patients with risk factors for hypercapnia but no prior history of respiratory acidosis
- adjust target range to 94-98% if the pCO2 is normal

Situations where oxygen therapy should not be used routinely if there is no evidence of hypoxia:
- myocardial infarction and acute coronary syndromes
- stroke
- obstetric emergencies
- anxiety-related hyperventilation

## SMOKING CESSATION

NICE released guidance in 2008 on the management of smoking cessation. General points include:

- patients should be offered nicotine replacement therapy (NRT), varenicline or bupropion - NICE state that clinicians should not favour one medication over another
- NRT, varenicline or bupropion should normally be prescribed as part of a commitment to stop smoking on or before a particular date (target stop date)
- prescription of NRT, varenicline or bupropion should be sufficient to last only until 2 weeks after the target stop date. Normally, this will be after 2 weeks of NRT therapy, and 3-4 weeks for varenicline and bupropion, to allow for the different methods of administration and mode of action. Further prescriptions should be given only to people who have demonstrated that their quit attempt is continuing
- if unsuccessful using NRT, varenicline or bupropion, do not offer a repeat prescription within 6 months unless special circumstances have intervened
- do not offer NRT, varenicline or bupropion in any combination

Nicotine replacement therapy

- adverse effects include nausea & vomiting, headaches and flu-like symptoms
- NICE recommend offering a combination of nicotine patches and another form of NRT (such as gum, inhalator, lozenge or nasal spray) to people who show a high level of dependence on nicotine or who have found single forms of NRT inadequate in the past

Varenicline

- a nicotinic receptor partial agonist
- should be started 1 week before the patients target date to stop
- the recommended course of treatment is 12 weeks (but patients should be monitored regularly and treatment only continued if not smoking)
- has been shown in studies to be more effective than bupropion
- nausea is the most common adverse effect. Other common problems include headache, insomnia, abnormal dreams
- varenicline should be used with caution in patients with a history of depression or self-harm. There are ongoing studies looking at the risk of suicidal behaviour in patients taking varenicline
- contraindicated in pregnancy and breast feeding

Bupropion

- a norepinephrine and dopamine reuptake inhibitor, and nicotinic antagonist
- should be started 1 to 2 weeks before the patients target date to stop
- small risk of seizures (1 in 1,000)
- contraindicated in epilepsy, pregnancy and breast feeding. Having an eating disorder is a relative contraindication

**Pregnant women**

NICE recommended in 2010 that all pregnant women should be tested for smoking using carbon monoxide detectors, partly because 'some women find it difficult to say that they smoke because the pressure not to smoke during pregnancy is so intense.'. All women who smoke, or have stopped smoking within the last 2 weeks, or those with a CO reading of 7 ppm or above should be referred to NHS Stop Smoking Services.

Interventions

- the first-line interventions in pregnancy should be cognitive behaviour therapy, motivational interviewing or structured self-help and support from NHS Stop Smoking Services
- the evidence for the use of NRT in pregnancy is mixed but it is often used if the above measures failure. There is no evidence that it affects the child's birthweight. Pregnant women should remove the patches before going to bed
- as mentioned above, varenicline and bupropion are contraindicated

# ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is caused by the increased permeability of alveolar capillaries leading to fluid accumulation in the alveoli, i.e. non-cardiogenic pulmonary oedema. It is a serious condition that has a mortality of around 40% and is associated with significant morbidity in those who survive.

Causes
- infection: sepsis, pneumonia
- massive blood transfusion
- trauma
- smoke inhalation
- acute pancreatitis
- cardio-pulmonary bypass

Clinical features are typically of an acute onset and severe:
- dyspnoea
- elevated respiratory rate
- bilateral lung crackles
- low oxygen saturations

A chest x-ray and arterial blood gases are the key investigations.

Criteria (American-European Consensus Conference)
- acute onset (within 1 week of a known risk factor)
- pulmonary oedema: bilateral infiltrates on chest x-ray ('not fully explained by effusions, lobar/lung collapse or nodules)
- non-cardiogenic (pulmonary artery wedge pressure needed if doubt)
- $pO_2/FiO_2 < 40$kPa (200 mmHg)

Management
- due to the severity of the condition patients are generally managed in ITU
- oxygenation/ventilation to treat the hypoxaemia
- general organ support e.g. vasopressors as needed
- treatment of the underlying cause e.g. antibiotics for sepsis
- certain strategies such as prone positioning and muscle relaxation have been shown to improve outcome in ARDS

# MIDDLE EAST RESPIRATORY SYNDROME

Middle East respiratory syndrome (MERS) is caused by the betacoronavirus MERS-CoV.

At the present time, MERS-CoV is limited to the Arabian Peninsula and its surrounding countries, although due to an incubation period of 2-14 days travellers returning from this region may present with MERS in other parts of the world.

Contact with camels (including camel products such as milk) is a significant risk factor for MERS-CoV.

The clinical syndrome of MERS is varied, ranging from very only mild symptoms through to life-threatening multi-organ failure.

# NON-INVASIVE VENTILATION

The British Thoracic Society (BTS) published guidelines in 2002 on the use of non-invasive ventilation in acute respiratory failure. Following these the Royal College of Physicians published guidelines in 2008.

Non-invasive ventilation - key indications
- COPD with respiratory acidosis pH 7.25-7.35*
- type II respiratory failure secondary to chest wall deformity, neuromuscular disease or obstructive sleep apnoea
- cardiogenic pulmonary oedema unresponsive to CPAP
- weaning from tracheal intubation

Recommended initial settings for bi-level pressure support in COPD
- Expiratory Positive Airway Pressure (EPAP): 4-5 cm $H_2O$
- Inspiratory Positive Airway Pressure (IPAP): RCP advocate 10 cm H20 whilst BTS suggest 12-15 cm $H_2O$
- back up rate: 15 breaths/min
- back up inspiration:expiration ratio: 1:3

*the BTS guidelines state that NIV can be used in patients who are more acidotic (i.e. $pH < 7.25$) but that a greater degree of monitoring is required (e.g. HDU) and a lower threshold for intubation and ventilation should be used

# PLEURAL EFFUSION: CAUSES

Pleural effusions may be classified as being either a transudate or exudate according to the protein concentration.

Transudate (< 30g/L protein)
- heart failure (most common transudate cause)
- hypoalbuminaemia (liver disease, nephrotic syndrome, malabsorption)
- hypothyroidism
- Meigs' syndrome

Exudate (> 30g/L protein)
- infection: pneumonia (most common exudate cause), TB, subphrenic abscess
- connective tissue disease: RA, SLE
- neoplasia: lung cancer, mesothelioma, metastases
- pancreatitis
- pulmonary embolism
- Dressler's syndrome
- yellow nail syndrome

Features
- dyspnoea, non-productive cough or chest pain are possible presenting symptoms
- classic examination findings include dullness to percussion, reduced breath sounds and reduced chest expansion

# PLEURAL EFFUSION: INVESTIGATION AND MANAGEMENT

The British Thoracic Society (BTS) produced guidelines in 2010 covering the investigation of patients with a pleural effusion.

Imaging
- posterioranterior (PA) chest x-rays should be performed in all patients
- ultrasound is recommended: it increases the likelihood of successful pleural aspiration and is sensitive for detecting pleural fluid septations
- contrast CT is now increasingly performed to investigate the underlying cause, particularly for exudative effusions

Pleural aspiration
- as above, ultrasound is recommended to reduce the complication rate
- a 21G needle and 50ml syringe should be used

- fluid should be sent for pH, protein, lactate dehydrogenase (LDH), cytology and microbiology

**Light's criteria** was developed in 1972 to help distinguish between a transudate and an exudate. The BTS recommend using the criteria for borderline cases:

- exudates have a protein level of >30 g/L, transudates have a protein level of <30 g/L
- if the protein level is between 25-35 g/L, Light's criteria should be applied. An exudate is likely if at least one of the following criteria are met:
  - pleural fluid protein divided by serum protein >0.5
  - pleural fluid LDH divided by serum LDH >0.6
  - pleural fluid LDH more than two-thirds the upper limits of normal serum LDH

Other characteristic pleural fluid findings:

- low glucose: rheumatoid arthritis, tuberculosis
- raised amylase: pancreatitis, oesophageal perforation
- heavy blood staining: mesothelioma, pulmonary embolism, tuberculosis

### Pleural infection

All patients with a pleural effusion in association with sepsis or a pneumonic illness require diagnostic pleural fluid sampling

- if the fluid is purulent or turbid/cloudy a chest tube should be placed to allow drainage
- if the fluid is clear but the **pH is less than 7.2 in patients with suspected pleural infection a chest tube should be placed**

### Management of recurrent pleural effusion

Options for managing patients with recurrent pleural effusions include:

- recurrent aspiration
- pleurodesis
- indwelling pleural catheter
- drug management to alleviate symptoms e.g. opioids to relieve dyspnoea

# PNEUMONIA: ASSESSMENT AND MANAGEMENT

**Primary care setting**

NICE recommends that patients should initially be assessed in primary care using the CRB65 criteria:

| Criterion | Marker |
|---|---|
| C | Confusion (abbreviated mental test score <= 8/10) |
| R | Respiration rate >= 30/min |
| B | Blood pressure: systolic <= 90 mmHg and/or diastolic <= 60 mmHg |
| 65 | Aged >= 65 years |

Patients are stratified for risk of death as follows:

- 0: low risk (less than 1% mortality risk)
- 1 or 2: intermediate risk (1-10% mortality risk)
- 3 or 4: high risk (more than 10% mortality risk).

NICE recommend, in conjunction with clinical judgement:

- for all other patients, particularly those with a CRB65 score of 2 or more.

NICE also mention point-of-care CRP test. This is currently not widely available but they make the following recommendation with reference to the use of antibiotic therapy:
CRP < 20 mg/L - do not routinely offer antibiotic therapy
CRP 20 - 100 mg/L - consider a delayed antibiotic prescription
CRP > 100 mg/L - offer antibiotic therapy

**Secondary care setting**

Note that in hospital, once blood tests are available the CURB65, rather than the CRB65, can be used. This adds an extra criterion of urea > 7 mmol/L:

| Criterion | Marker |
|---|---|
| C | Confusion (abbreviated mental test score <= 8/10) |
| U | urea > 7 mmol/L |
| R | Respiration rate >= 30/min |
| B | Blood pressure: systolic <= 90 mmHg and/or diastolic <= 60 mmHg |
| 65 | Aged >= 65 years |

NICE recommend, in conjunction with clinical judgement:

- consider home-based care for patients with a CURB65 score of 0 or 1 - low risk (less than 3% mortality risk)

- consider hospital-based care for patients with a CURB65 score of 2 or more - intermediate risk (3-15% mortality risk)
- consider intensive care assessment for patients with a CURB65 score of 3 or more - high risk (more than 15% mortality risk)

Investigations
- chest x-ray
- in intermediate or high-risk patients NICE recommend blood and sputum cultures, pneumococcal and legionella urinary antigen tests
- CRP monitoring is recommend for admitted patients to help determine response to treatment

Management of low-severity community acquired pneumonia
- amoxicillin is first-line
- if penicillin allergic then use a macrolide or tetracycline
- NICE now recommend a 5 day course of antibiotics for patients with low severity community acquired pneumonia

Management of moderate and high-severity community acquired pneumonia
- dual antibiotic therapy is recommended with amoxicillin and a macrolide
- a 7-10 day course is recommended
- NICE recommend considering a beta-lactamase stable penicillin such as co-amoxiclav, ceftriaxone or piperacillin with tazobactam and a macrolide in high-severity community acquired pneumonia

**Discharge criteria and advice post-discharge**

NICE recommend that patients are not routinely discharged if in the past 24 hours they have had 2 or more of the following findings:
- temperature higher than 37.5°C
- respiratory rate 24 breaths per minute or more
- heart rate over 100 beats per minute
- systolic blood pressure 90 mmHg or less
- oxygen saturation under 90% on room air
- abnormal mental status
- inability to eat without assistance.

They also recommend delaying discharge if the temperature is higher than 37.5°C.

NICE recommend that the following information is given to patients with pneumonia in terms of how quickly their symptoms should symptoms should resolve:

| Time | Progress |
|---|---|
| 1 week | Fever should have resolved |
| 4 weeks | Chest pain and sputum production should have substantially reduced |

| Time | Progress |
|---|---|
| 6 weeks | Cough and breathlessness should have substantially reduced |
| 3 months | Most symptoms should have resolved but fatigue may still be present |
| 6 months | Most people will feel back to normal. |

# KLEBSIELLA

Klebsiella pneumoniae is a Gram-negative rod that is part of the normal gut flora. It can cause a number of infections in humans including pneumonia (typically following aspiration) and urinary tract infections.

Features of Klebsiella pneumonia

- more common in alcoholic and diabetics
- may occur following aspiration
- 'red-currant jelly' sputum
- often affects upper lobes

Prognosis

- commonly causes lung abscess formation and empyema
- mortality is 30-50%

A human neutrophil interacting with *Klebsiella pneumoniae* (pink), a multidrug-resistant bacterium that causes severe hospital infections. Credit: NIAID

# CRYPTOGENIC ORGANIZING PNEUMONIA

Cryptogenic organizing pneumonia (COP) is a diffuse interstitial lung disease that affects the distal bronchioles, respiratory bronchioles, alveolar ducts and alveolar walls. It affects around 2 people per 100,000. The aetiology is unknown.

Males and females are equally affected and tend to present in the 5th or 6th decade of life and is not associated with smoking. Patients typically present with a cough, shortness of breath, fever and malaise. Symptoms can be present for weeks or months. There is often a history of non-response to antibiotics. Haemoptysis is rare. Clinical examination is often normal but inspiratory crackles can be heard. Wheeze and clubbing are rare.

Bloods show a leukocytosis and an elevated ESR and CRP. Imaging typically shows bilateral patchy or diffuse consolidative or ground glass opacities. Lung function tests are most commonly restrictive but can be obstructive or normal. The transfer factor is reduced.

Treatment is watch and wait if mild or high dose oral steroids if severe.

# PSITTACOSIS

Psittacosis is infection caused by Chlamydia psittaci. The most common presentation is as a cause of atypical pneumonia. Psittacosis should be suspected in a combination of typical fever with a history of bird contact (reported in 84%) or a presentation with pneumonia and severe headache or organomegaly and failure to respond to penicillin-based antibiotics.

Epidemiology
- Psittacosis is present throughout the world, including the United Kingdom
- It is more common in young adults

Pathology
- Chlamydia psittaci is an obligate intracellular bacterium
- Transmission is typically from birds or bird secretions including urine and faeces, typically occurring after cleaning bird cages
- Many birds have been implicated in transmission, including pet birds and wild birds
- Transmission from other animals or humans is possible but very rare and no strong female or male predisposition has been noted
- It is rare; in the US there are roughly 10 cases reported annually

Patients typically present with a subacute onset of:

- Flu-like symptoms (90%): fever, headache and myalgia
- Respiratory symptoms (82%): dyspnoea, dry cough and chest pain

Signs:
- Chest: unilateral crepitations and vesicular breathing (common), evidence of pleural effusion (uncommon)
- Abdomen: hepatomegaly and splenomegaly (rare)

Investigations:
- Raised inflammatory markers
- Chest X-ray: consolidation (90%)
- Confirmation with serology (usually as part of atypical pneumonia screening)

Treatment:
- 1st-line: tetracyclines e.g. doxycycline
- 2nd-line: macrolides e.g. erythromycin

# TUBERCULOSIS

Tuberculosis (TB) is an infection caused by Mycobacterium tuberculosis that most commonly affects the lungs. Understanding the pathophysiology of TB can be difficult - the key is to differentiate between primary and secondary disease.

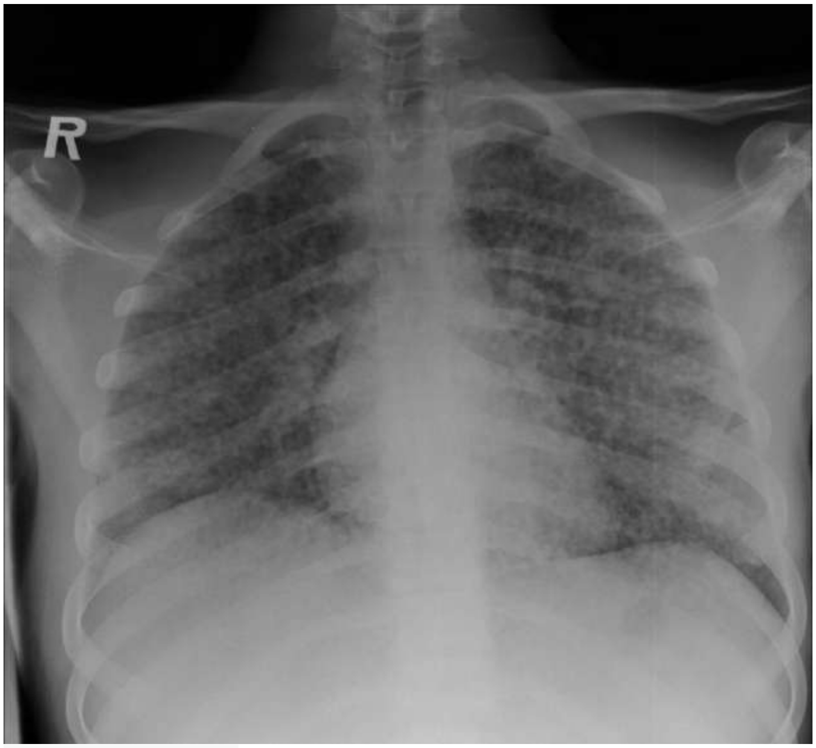
**Primary tuberculosis**
A non-immune host who is exposed to M. tuberculosis may develop primary infection of the lungs. A small lung lesion known as a Ghon focus develops. The Ghon focus is composed of tubercle-laden macrophages. The combination of a Ghon focus and hilar lymph nodes is known as a Ghon complex

In immunocompotent people the intially lesion usually heals by fibrosis. Those who are immunocompromised may develop disseminated disease (miliary tuberculosis).

**Secondary (post-primary) tuberculosis**
If the host becomes immunocompromised the initial infection may become reactivated. Reactivation generally occurs in the apex of the lungs and may spread locally or to more distant sites. Possible causes of immunocomprise include:
- immunosuppressive drugs including steroids
- HIV
- malnutrition

The lungs remain the most common site for secondary tuberculosis. Extra-pulmonary infection may occur in the following areas:
- central nervous system (tuberculous meningitis - the most serious complication)

- vertebral bodies (Pott's disease)
- cervical lymph nodes (scrofuloderma)
- renal
- gastrointestinal tract



Miliary tuberculosis

Scanning electron micrograph of Mycobacterium tuberculosis bacteria, which cause TB. Credit: NIAID

# PNEUMOTHORAX: FEATURES

Risk factors
- pre-existing lung disease: COPD, asthma, cystic fibrosis, lung cancer, Pneumocystis pneumonia
- connective tissue disease: Marfan's syndrome, rheumatoid arthritis
- ventilation, including non-invasive ventilation
- catamenial pneumothorax is the cause of 3-6% of spontaneous pneumothoraces occurring in menstruating women. It is thought to be caused by endometriosis within the thorax

Symptoms tend to come on suddenly. Features include:
- dyspnoea
- chest pain: often pleuritic
- sweating
- tachypnoea
- tachycardia

# PNEUMOTHORAX: MANAGEMENT

The British Thoracic Society (BTS) published updated guidelines for the management of spontaneous pneumothorax in 2010. A pneumothorax is termed primary if there is no underlying lung disease and secondary if there is.

**Primary pneumothorax**
Recommendations include:
- if the rim of air is < 2cm and the patient is not short of breath then discharge should be considered
- otherwise aspiration should be attempted
- if this fails (defined as > 2 cm or still short of breath) then a chest drain should be inserted
- patients should be advised to avoid smoking to reduce the risk of further episodes - the lifetime risk of developing a pneumothorax in healthy smoking men is around 10% compared with around 0.1% in non-smoking men

**Secondary pneumothorax**
Recommendations include:
- if the patient is > 50 years old and the rim of air is > 2cm and/or the patient is short of breath then a chest drain should be inserted.
- otherwise aspiration should be attempted if the rim of air is between 1-2cm. If aspiration fails (i.e. pneumothorax is still greater then 1cm) a chest drain should be inserted. All patients should be admitted for at least 24 hours

- if the pneumothorax is less the 1cm then the BTS guidelines suggest giving oxygen and admitting for 24 hours
- regarding scuba diving, the BTS guidelines state: 'Diving should be permanently avoided unless the patient has undergone bilateral surgical pleurectomy and has normal lung function and chest CT scan postoperatively.'

**Iatrogenic pneumothorax**
Recommendations include:
- less likelihood of recurrence than spontaneous pneumothorax
- majority will resolve with observation, if treatment is required then aspiration should be used
- ventilated patients need chest drains, as may some patients with COPD

# CHEST DRAIN

A chest drain is a tube inserted into the pleural cavity which creates a one-way valve, allowing movement of air or liquid out of the cavity.

Chest drain insertion is indicated in cases of:
- Pleural effusion
- Pneumothorax not suitable for conservative management or aspiration
- Empyema
- Haemothorax
- Haemopneumothorax
- Chylothorax
- In some cases of penetrating chest wall injury in ventilated patients

Insertion of a chest drain is relatively contraindicated in patients with any of the following:
- INR > 1.3
- Platelet count < 75
- Pulmonary bullae
- Pleural adhesions

Please note, all of the above represent only relative contraindications, addressing respiratory compromise in an emergency situation should always be on an individual case basis.

Once patient consent has been obtained and patient imaging assessed, the patient should be positioned in a supine position or at a 45º angle. The patient's forearm may be positioned behind the patient's head to allow easy access to the axilla. Identify the 5th intercostal space in the midaxillary line. Alternatively, positioning may be determined by ultrasound guidance, British Thoracic Society Guidance 'strongly recommend' use of ultrasound guidance in all cases of fluid within the pleura. The area should be anaesthetised using local anaesthetic injection (lidocaine, up to 3mg/kg). The drainage tube should then be inserted using a Seldinger technique. The drain tubing should then be secured using either a straight stitch or with an adhesive dressing.

Positioning can be confirmed by aspiration of fluid from the drainage tubing, by 'swinging' of the fluid within the drain tubing when the patient inspires and on chest x-ray.

Complications that may occur and which the patient should be advised of in the process of obtaining consent:

- Failure of insertion - the drain may be abutting the apical pleura, in which case it should be pulled back, or may be subcutaneous or in rare cases could enter the abdominal cavity. In both latter cases, the drain should be removed and re-sited.
- Bleeding - around the site of the drain or into the pleural space
- Infection
- Penetration of the lung
- Re-expansion pulmonary oedema

Re-expansion pulmonary oedema may be preceded by the onset of a cough and/or shortness of breath. In the event of concerns regarding re-expansion pulmonary oedema, the chest drain should be clamped and an urgent chest x-ray should be obtained. To avoid re-expansion pulmonary oedema, it is recommended that the drain tubing should be clamped regularly in the event of rapid fluid output i.e. drain output should not exceed 1L of fluid over a short period of time (less than 6 hours).

Removal of the chest drain is dependent upon the indication for insertion:

- In cases of fluid drainage from the pleural cavity, the drain should be removed when there has been no output for > 24 hours and imaging shows resolution of the fluid collection.
- In cases of pneumothorax, the drain should be removed when it is no longer bubbling spontaneously or when the patient coughs and ideally when imaging shows resolution of the pneumothorax.
- Drains inserted in cases of penetrating chest injury should be reviewed by the specialist to confirm an appropriate time for removal.

# OBSTRUCTIVE SLEEP APNOEA/HYPOPNOEA SYNDROME

Predisposing factors

- obesity
- macroglossia: acromegaly, hypothyroidism, amyloidosis
- large tonsils
- Marfan's syndrome

The partner often complains of excessive snoring and may report periods of apnoea.

Consequence

- daytime somnolence
- compensated respiratory acidosis
- hypertension

Assessment of sleepiness

- Epworth Sleepiness Scale - questionnaire completed by patient +/- partner
- Multiple Sleep Latency Test (MSLT) - measures the time to fall asleep in a dark room (using EEG criteria)

Diagnostic tests

- sleep studies (polysomnography) - ranging from monitoring of pulse oximetry at night to full polysomnography where a wide variety of physiological factors are measured including EEG, respiratory airflow, thoraco-abdominal movement, snoring and pulse oximetry

Management

- weight loss
- continuous positive airway pressure (CPAP) is first line for moderate or severe OSAHS
- intra-oral devices (e.g. mandibular advancement) may be used if CPAP is not tolerated or for patients with mild OSAHS where there is no daytime sleepiness
- the DVLA should be informed if OSAHS is causing excessive daytime sleepiness
- limited evidence to support use of pharmacological agents

# PULMONARY HYPERTENSION: CAUSES AND CLASSIFICATION

Pulmonary hypertension may be defined as a sustained elevation in mean pulmonary arterial pressure of greater than 25 mmHg at rest. It has recently been reclassified by the WHO:

Group 1: Pulmonary arterial hypertension (PAH)
- idiopathic*
- familial
- associated conditions: collagen vascular disease, congenital heart disease with systemic to pulmonary shunts, HIV**, drugs and toxins, sickle cell disease
- persistent pulmonary hypertension of the newborn

Group 2: Pulmonary hypertension with left heart disease
- left-sided atrial, ventricular or valvular disease such as left ventricular systolic and diastolic dysfunction, mitral stenosis and mitral regurgitation

Group 3: Pulmonary hypertension secondary to lung disease/hypoxia
- COPD
- interstitial lung disease
- sleep apnoea
- high altitude

Group 4: Pulmonary hypertension due to thromboembolic disease

Group 5: Miscellaneous conditions
- lymphangiomatosis e.g. secondary to carcinomatosis or sarcoidosis

*previously termed primary pulmonary hypertension
**the mechanism by which HIV infection produces pulmonary hypertension remains unknown

# ALPHA-1 ANTITRYPSIN DEFICIENCY

Alpha-1 antitrypsin (A1AT) deficiency is a common inherited condition caused by a lack of a protease inhibitor (Pi) normally produced by the liver. The role of A1AT is to protect cells from enzymes such as neutrophil elastase. It classically causes emphysema (i.e. chronic obstructive pulmonary disease) in patients who are young and non-smokers.

Genetics

- located on chromosome 14
- inherited in an autosomal recessive / co-dominant fashion*
- alleles classified by their electrophoretic mobility - M for normal, S for slow, and Z for very slow
- normal = PiMM
- homozygous PiSS (50% normal A1AT levels)
- homozygous PiZZ (10% normal A1AT levels)

Features

- patients who manifest disease usually have PiZZ genotype
- lungs: panacinar emphysema, most marked in lower lobes
- liver: cirrhosis and hepatocellular carcinoma in adults, cholestasis in children

Investigations

- A1AT concentrations
- spirometry: obstructive picture

Management

- no smoking
- supportive: bronchodilators, physiotherapy
- intravenous alpha1-antitrypsin protein concentrates
- surgery: lung volume reduction surgery, lung transplantation

*trusted sources are split on which is a more accurate description

# KARTAGENER'S SYNDROME

Kartagener's syndrome (also known as primary ciliary dyskinesia) was first described in 1933 and most frequently occurs in examinations due to its association with dextrocardia (e.g. 'quiet heart sounds', 'small volume complexes in lateral leads')

Pathogenesis

- dynein arm defect results in immotile cilia

Features

- dextrocardia or complete situs inversus
- bronchiectasis
- recurrent sinusitis
- subfertility (secondary to diminished sperm motility and defective ciliary action in the fallopian tubes)

## LOFGREN'S SYNDROME

Lofgren's syndrome is an acute form sarcoidosis characterised by bilateral hilar lymphadenopathy (BHL), erythema nodosum, fever and polyarthralgia.

It typically occurs in young females and carries an excellent prognosis.

# ATELECTASIS

Atelectasis is a common postoperative complication in which basal alveolar collapse can lead to respiratory difficulty. It is caused when airways become obstructed by bronchial secretions.

Features

- it should be suspected in the presentation of dyspnoea and hypoxaemia around 72 hours postoperatively

Management

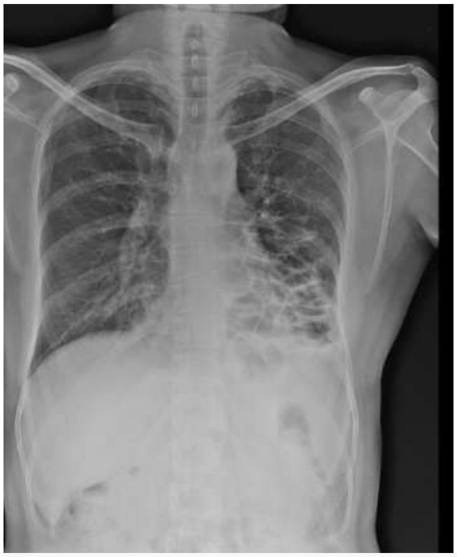
- positioning the patient upright
- chest physiotherapy: breathing exercises

# BRONCHIECTASIS: CAUSES

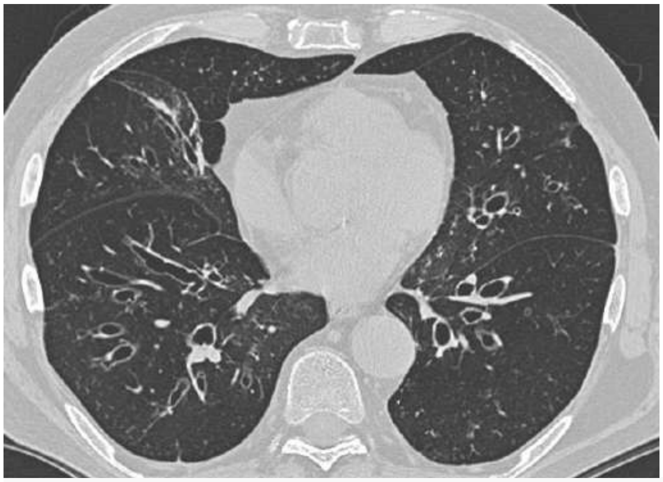
Bronchiectasis describes a permanent dilatation of the airways secondary to chronic infection or inflammation. There are a wide variety of causes are listed below:

Causes

- post-infective: tuberculosis, measles, pertussis, pneumonia
- cystic fibrosis
- bronchial obstruction e.g. lung cancer/foreign body
- immune deficiency: selective IgA, hypogammaglobulinaemia
- allergic bronchopulmonary aspergillosis (ABPA)
- ciliary dyskinetic syndromes: Kartagener's syndrome, Young's syndrome
- yellow nail syndrome



Chest x-ray showing tramlines, most prominent in the left lower zone


CT chest showing widespread tram-track and signet ring signs

# BRONCHIECTASIS: MANAGEMENT

Bronchiectasis describes a permanent dilatation of the airways secondary to chronic infection or inflammation. After assessing for treatable causes (e.g. immune deficiency) management is as follows:

- physical training (e.g. inspiratory muscle training) - has a good evidence base for patients with non-cystic fibrosis bronchiectasis
- postural drainage
- antibiotics for exacerbations + long-term rotating antibiotics in severe cases
- bronchodilators in selected cases
- immunisations
- surgery in selected cases (e.g. Localised disease)

Most common organisms isolated from patients with bronchiectasis:

- Haemophilus influenzae (most common)
- Pseudomonas aeruginosa
- Klebsiella spp.
- Streptococcus pneumoniae

# LUNG CANCER: RISK FACTORS

Smoking
- increases risk of lung ca by a factor of 10

Other factors
- asbestos - increases risk of lung ca by a factor of 5
- arsenic
- radon
- nickel
- chromate
- aromatic hydrocarbon
- cryptogenic fibrosing alveolitis

Factors that are NOT related
- coal dust

Smoking and asbestos are synergistic, i.e. a smoker with asbestos exposure has a 10 * 5 = 50 times increased risk

# LUNG CANCER: INVESTIGATION

Chest x-ray
- this is often the first investigation done in patients with suspected lung cancer
- in around 10% of patients subsequently diagnosed with lung cancer the chest x-ray was reported as normal

CT
- is the investigation of choice to investigate suspected lung cancer

Bronchoscopy
- this allows a biopsy to be taken to obtain a histological diagnosis sometimes aided by endobronchial ultrasound

PET scanning
- is typically done in non-small cell lung cancer to establish eligibility for curative treatment
- uses 18-fluorodeoxygenase which is preferentially taken up by neoplastic tissue
- has been shown to improve diagnostic sensitivity of both local and distant metastasis spread in non-small cell lung cancer

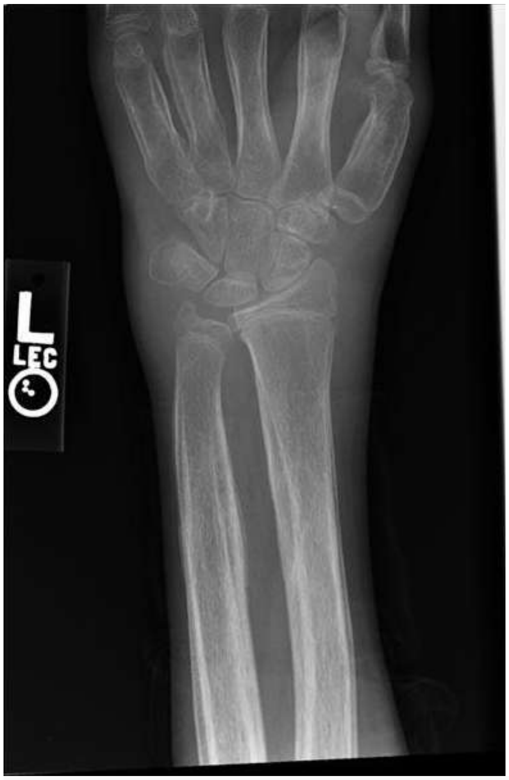
Bloods
- raised platelets may be seen

# LUNG CANCER: PARANEOPLASTIC FEATURES

Small cell
- ADH
- ACTH - not typical, hypertension, hyperglycaemia, hypokalaemia, alkalosis and muscle weakness are more common than buffalo hump etc
- Lambert-Eaton syndrome

Squamous cell
- parathyroid hormone-related protein (PTH-rp) secretion causing hypercalcaemia
- clubbing
- hypertrophic pulmonary osteoarthropathy (HPOA)
- hyperthyroidism due to ectopic TSH

Adenocarcinoma
- gynaecomastia
- hypertrophic pulmonary osteoarthropathy (HPOA)



Hypertrophic pulmonary osteoarthropathy is a proliferative periostisis involving that typically involves the long bones. It is often painful.

*whilst it is traditionally taught that HPOA is most common with squamous cell carcinoma some studies indicate that adenocarcinoma is the most common cause e.g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4049689/

## LUNG CANCER: NON-SMALL CELL MANAGEMENT

Management
- only 20% suitable for surgery
- mediastinoscopy performed prior to surgery as CT does not always show mediastinal lymph node involvement
- curative or palliative radiotherapy
- poor response to chemotherapy

Surgery contraindications
- assess general health
- stage IIIb or IV (i.e. metastases present)
- FEV1 < 1.5 litres is considered a general cut-off point*
- malignant pleural effusion
- tumour near hilum
- vocal cord paralysis
- SVC obstruction

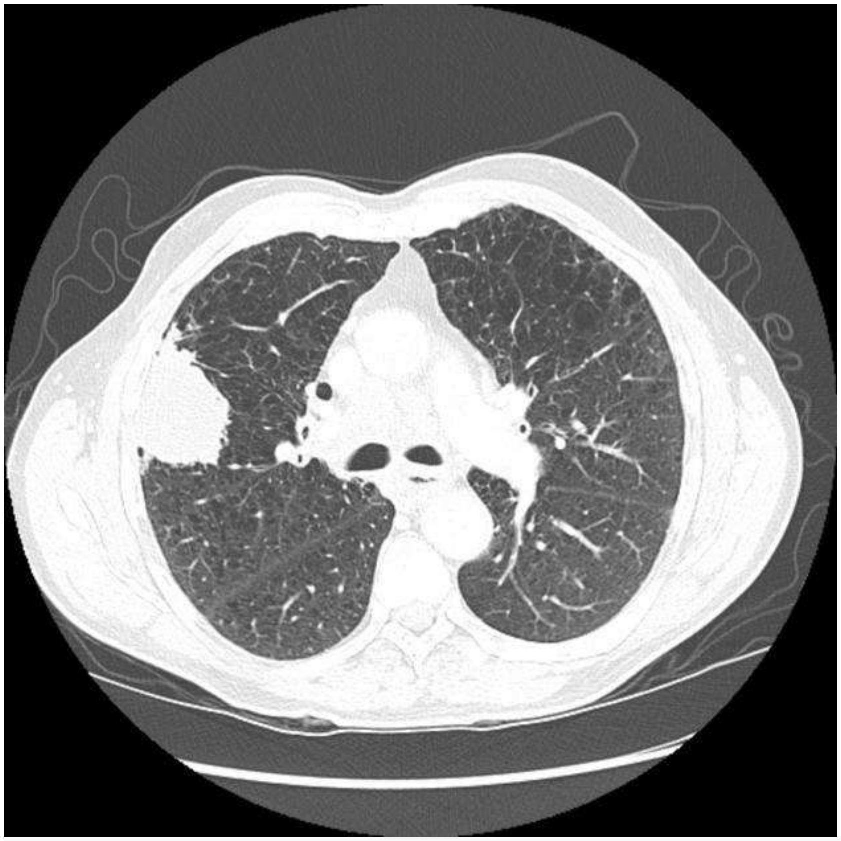
* However if FEV1 < 1.5 for lobectomy or < 2.0 for pneumonectomy then some authorities advocate further lung function tests as operations may still go ahead based on the results

## LUNG CANCER: SMALL CELL

Features
- usually central
- arise from APUD* cells
- associated with ectopic ADH, ACTH secretion
- ADH → hyponatraemia
- ACTH → Cushing's syndrome
- ACTH secretion can cause bilateral adrenal hyperplasia, the high levels of cortisol can lead to hypokalaemic alkalosis
- Lambert-Eaton syndrome: antibodies to voltage gated calcium channels causing myasthenic like syndrome

Management

- usually metastatic disease by time of diagnosis
- patients with very early stage disease (T1-2a, N0, M0) are now considered for surgery. NICE support this approach in their 2011 guidelines
- however, most patients with limited disease receive a combination of chemotherapy and radiotherapy
- patients with more extensive disease are offered palliative chemotherapy



CT scan showing small cell lung cancer with multiple pulmonary nodules and extensive mediastinal nodal metastases.

*an acronym for

- Amine - high amine content
- Precursor Uptake - high uptake of amine precursors
- Decarboxylase - high content of the enzyme decarboxylase

## LUNG CANCER: CARCINOID

The vast majority of bronchial adenomas are carcinoid tumours, arising from the amine precursor uptake and decarboxylation (APUD) system, like small cell tumours. Lung carcinoid accounts 1% of lung tumours and for 10% of carcinoid tumours. The term bronchial adenoma is being phased out.

Lung carcinoid

- typical age = 40-50 years
- smoking not risk factor
- slow growing: e.g. long history of cough, recurrent haemoptysis
- often centrally located and not seen on CXR
- 'cherry red ball' often seen on bronchoscopy
- carcinoid syndrome itself is rare (associated with liver metastases)

Management
- surgical resection
- if no metastases then 90% survival at 5 years

## LUNG CANCER: REFERRAL

The 2015 NICE cancer referral guidelines gave the following advice:

Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they:
- have chest x-ray findings that suggest lung cancer
- are aged 40 and over with unexplained haemoptysis

Offer an urgent chest x-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over if they have 2 or more of the following unexplained symptoms, or if they have ever smoked and have 1 or more of the following unexplained symptoms:
- cough
- fatigue
- shortness of breath
- chest pain
- weight loss
- appetite loss

Consider an urgent chest x-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over with any of the following:
- persistent or recurrent chest infection
- finger clubbing
- supraclavicular lymphadenopathy or persistent cervical lymphadenopathy
- chest signs consistent with lung cancer
- thrombocytosis

# SARCOIDOSIS

Sarcoidosis is a multisystem disorder of unknown aetiology characterised by non-caseating granulomas. It is more common in young adults and in people of African descent

Features

- acute: erythema nodosum, bilateral hilar lymphadenopathy, swinging fever, polyarthralgia
- insidious: dyspnoea, non-productive cough, malaise, weight loss
- skin: lupus pernio
- hypercalcaemia: macrophages inside the granulomas cause an increased conversion of vitamin D to its active form (1,25-dihydroxycholecalciferol)

**Syndromes associated with sarcoidosis**
**Lofgren's syndrome** is an acute form of the disease characterised by bilateral hilar lymphadenopathy (BHL), erythema nodosum, fever and polyarthralgia. It usually carries an excellent prognosis

In **Mikulicz syndrome*** there is enlargement of the parotid and lacrimal glands due to sarcoidosis, tuberculosis or lymphoma

**Heerfordt's syndrome** (uveoparotid fever) there is parotid enlargement, fever and uveitis secondary to sarcoidosis

*this term is now considered outdated and unhelpful by many as there is a confusing overlap with Sjogren's syndrome

# BILATERAL HILAR LYMPHADENOPATHY

The most common causes of bilateral hilar lymphadenopathy are sarcoidosis and tuberculosis.

Other causes include:

- lymphoma/other malignancy
- pneumoconiosis e.g. berylliosis
- fungi e.g. histoplasmosis, coccidioidomycosis

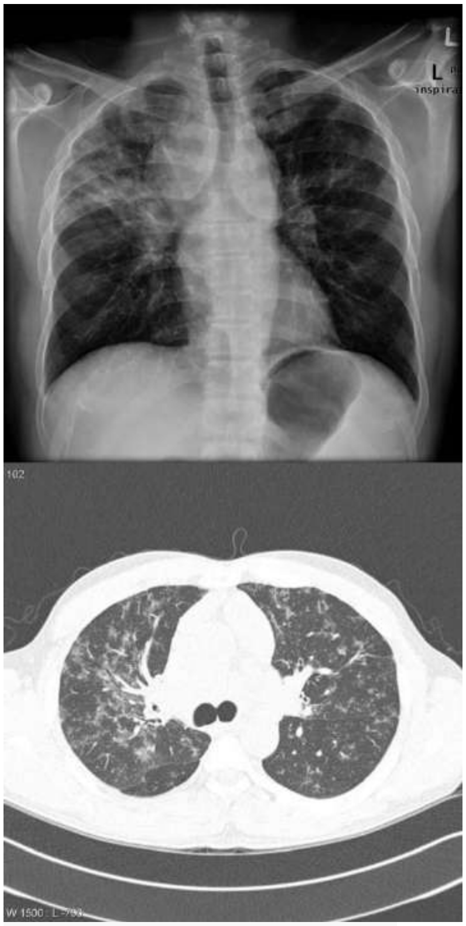
# SARCOIDOSIS: INVESTIGATION

There is no one diagnostic test for sarcoidosis and hence diagnosis is still largely clinical. ACE levels have a sensitivity of 60% and specificity of 70% and are therefore not reliable in the diagnosis of sarcoidosis although they may have a role in monitoring disease activity. Routine bloods may show hypercalcaemia (seen in 10% if patients) and a raised ESR

A chest x-ray may show the following changes:
stage 0 = normal
stage 1 = bilateral hilar lymphadenopathy (BHL)
stage 2 = BHL + interstitial infiltrates
stage 3 = diffuse interstitial infiltrates only
stage 4 = diffuse fibrosis

Other investigations*

- spirometry: may show a restrictive defect
- tissue biopsy: non-caseating granulomas
- gallium-67 scan - not used routinely



Chest x-ray and CT scan showing **stage 2** sarcoidosis with both bilateral hilar lymphadenopathy + interstitial infiltrates. The reticulonodular opacities are particularly noted in the upper zones. Remember that pulmonary fibrosis (which this case has not yet progressed to) may be divided into conditions which predominately affect the upper zones and those which predominately affect the lower zones - sarcoidosis is one of the former. The CT of the chest demonstrates diffuse areas of nodularity predominantly in a peribronchial distribution with patchy areas of consolidation particularly in the upper lobes. There is some surrounding ground glass opacities. No gross reticular changes to suggest fibrosis.

*the Kveim test (where part of the spleen from a patient with known sarcoidosis is injected under the skin) is no longer performed due to concerns about cross-infection

## SARCOIDOSIS: MANAGEMENT

Sarcoidosis is a multisystem disorder of unknown aetiology characterised by non-caseating granulomas. It is more common in young adults and in people of African descent.

Indications for steroids

- patients with chest x-ray stage 2 or 3 disease who are symptomatic. Patients with asymptomatic and stable stage 2 or 3 disease who have only mildly abnormal lung function do not require treatment
- hypercalcaemia
- eye, heart or neuro involvement

## SARCOIDOSIS: PROGNOSTIC FEATURES

Sarcoidosis is a multisystem disorder of unknown aetiology characterised by non-caseating granulomas. It is more common in young adults and in people of African descent. Sarcoidosis remits without treatment in approximately two-thirds of people

Factors associated with poor prognosis

- insidious onset, symptoms > 6 months
- absence of erythema nodosum
- extrapulmonary manifestations: e.g. lupus pernio, splenomegaly
- CXR: stage III-IV features
- black people

## SILICOSIS

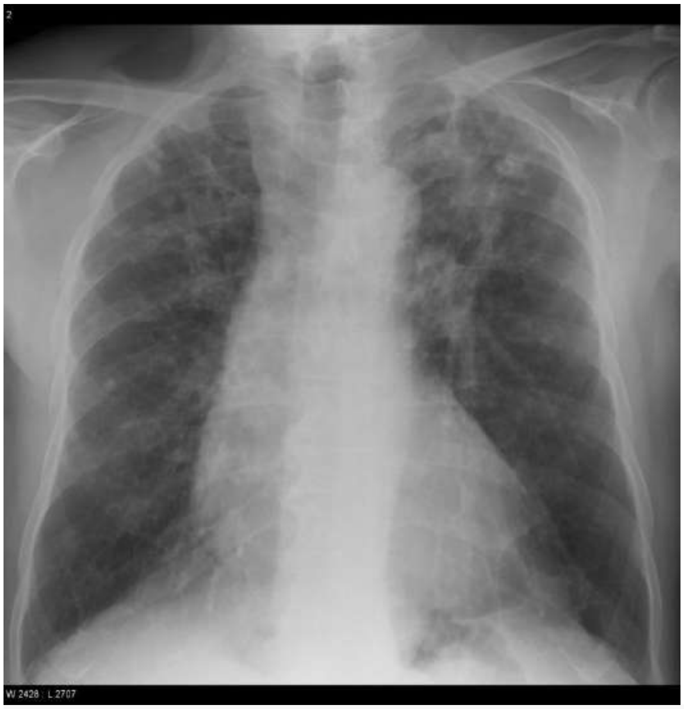
Silicosis is a fibrosing lung disease caused by the inhalation of fine particles of crystalline silicon dioxide (silica). It is a risk factor for developing TB (silica is toxic to macrophages).

Occupations at risk of silicosis

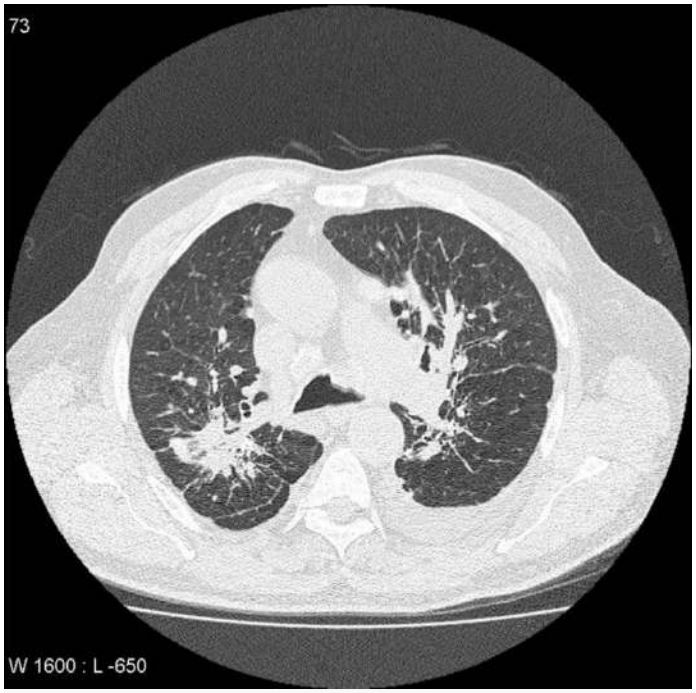
- mining
- slate works
- foundries
- potteries

Features

- fibrosing lung disease
- 'egg-shell' calcification of the hilar lymph nodes



Chest x-ray from a patient with silicosis. Note the bilateral diffuse upper lobe reticular shadowing superimposed with occasional scattered mass like opacities. These features are in keeping with silicosis and progressive massive fibrosis (PMF)



CT scan from a patient with silicosis showing upper zone predominant mass-like scarring with calcification and volume loss. Hilar and mediastinal lymph node calcification also noted. No cavitary changes are seen. There is a left pleural effusion.

# ASBESTOS AND THE LUNG

Asbestos can cause a variety of lung disease from benign pleural plaques to mesothelioma.

**Pleural plaques**
Pleural plaques are benign and do not undergo malignant change. They are the most common form of asbestos related lung disease and generally occur after a latent period of 20-40 years.

**Pleural thickening**
Asbestos exposure may cause diffuse pleural thickening in a similar pattern to that seen following an empyema or haemothorax. The underlying pathophysiology is not fully understood.

**Asbestosis**
The severity of asbestosis is related to the length of exposure. This is in contrast to mesothelioma where even very limited exposure can cause disease. The latent period is typically 15-30 years. Asbestosis typically causes lower lobe fibrosis. As with other forms of lung fibrosis the most common symptoms are shortness-of-breath and reduced exercise tolerance.

**Mesothelioma**
Mesothelioma is a malignant disease of the pleura. Crocidolite (blue) asbestos is the most dangerous form.

Possible features

- progressive shortness-of-breath
- chest pain
- pleural effusion

Patients are usually offered palliative chemotherapy and there is also a limited role for surgery and radiotherapy. Unfortunately the prognosis is very poor, with a median survival from diagnosis of 8-14 months.

**Lung cancer**
Asbestos exposure is a risk factor for lung cancer and also has a synergistic effect with cigarette smoke.

# MESOTHELIOMA

Mesothelioma is a cancer of the mesothelial layer of the pleural cavity that is strongly associated with asbestos exposure. In a small percentage of cases, other mesothelial layers such as those in the abdomen may be affected.

Features
- Dyspnoea, weight loss, chest wall pain
- Clubbing
- 30% present as painless pleural effusion
- Only 20% have pre-existing asbestosis
- History of asbestos exposure in 85-90%, latent period of 30-40 years

Basics
- Malignancy of mesothelial cells of pleura
- Metastases to contralateral lung and peritoneum
- Right lung affected more often than left

Investigation/diagnosis
- suspicion is normally raised by a chest x-ray showing either a pleural effusion or pleural thickening
- the next step is normally a pleural CT
- if a pleural effusion is present fluid should be sent for MC&S, biochemistry and cytology (but cytology is only helpful in 20-30% of cases)
- local anaesthetic thoracoscopy is increasingly used to investigate cytology negative exudative effusions as it has a high diagnostic yield (around 95%)
- if an area of pleural nodularity is seen on CT then an image-guided pleural biopsy may be used

Management
- Symptomatic
- Industrial compensation
- Chemotherapy, Surgery if operable
- Prognosis poor, median survival 12 months

# **RHEUMATOID ARTHRITIS: RESPIRATORY MANIFESTATIONS**

A variety of respiratory problems may be seen in patients with rheumatoid arthritis:
- pulmonary fibrosis
- pleural effusion
- pulmonary nodules
- bronchiolitis obliterans
- complications of drug therapy e.g. methotrexate pneumonitis
- pleurisy
- Caplan's syndrome - massive fibrotic nodules with occupational coal dust exposure
- infection (possibly atypical) secondary to immunosuppression

# LUNG FIBROSIS

It is important in the exam to be able to differentiate between conditions causing predominately upper or lower zone fibrosis. It should be noted that the more common causes (idiopathic pulmonary fibrosis, drugs) tend to affect the lower zones

Fibrosis predominately affecting the upper zones
hypersensitivity pneumonitis (also known as extrinsic allergic alveolitis)
coal worker's pneumoconiosis/progressive massive fibrosis
silicosis
sarcoidosis
ankylosing spondylitis (rare)
histiocytosis
tuberculosis

Fibrosis predominately affecting the lower zones
idiopathic pulmonary fibrosis
most connective tissue disorders (except ankylosing spondylitis) e.g. SLE
drug-induced: amiodarone, bleomycin, methotrexate
asbestosis

Acronym for causes of upper zone fibrosis:
CHARTS

- C - Coal worker's pneumoconiosis
- H - Histiocytosis/ hypersensitivity pneumonitis
- A - Ankylosing spondylitis
- R - Radiation
- T - Tuberculosis
- S - Silicosis/sarcoidosis

# IDIOPATHIC PULMONARY FIBROSIS

Idiopathic pulmonary fibrosis (IPF, previously termed cryptogenic fibrosing alveolitis) is a chronic lung condition characterised by progressive fibrosis of the interstitium of the lungs. Whilst there are many causes of lung fibrosis (e.g. medications, connective tissue disease, asbestos) the term IPF is reserved when no underlying cause exists.

IPF is typically seen in patients aged 50-70 years and is twice as common in men.

Features

- progressive exertional dyspnoea

- bibasal fine end-inspiratory crepitations on auscultation
- dry cough
- clubbing

Diagnosis

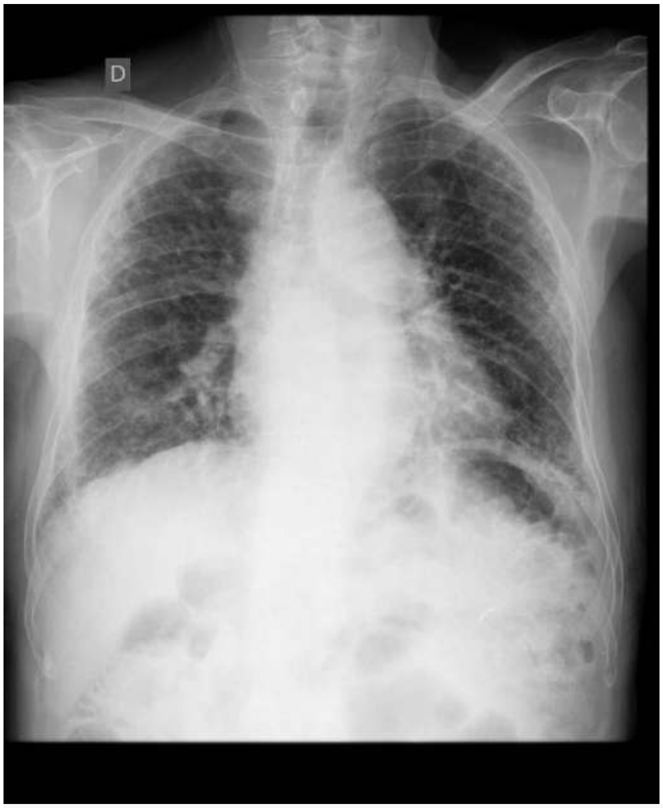
- spirometry: classically a restrictive picture (FEV1 normal/decreased, FVC decreased, FEV1/FVC increased)
- impaired gas exchange: reduced transfer factor (TLCO)
- imaging: bilateral interstitial shadowing (typically small, irregular, peripheral opacities - 'ground-glass' - later progressing to 'honeycombing') may be seen on a chest x-ray but high-resolution CT scanning is the investigation of choice and required to make a diagnosis of IPF
- ANA positive in 30%, rheumatoid factor positive in 10% but this does not necessarily mean that the fibrosis is secondary to a connective tissue disease. Titres are usually low

Management

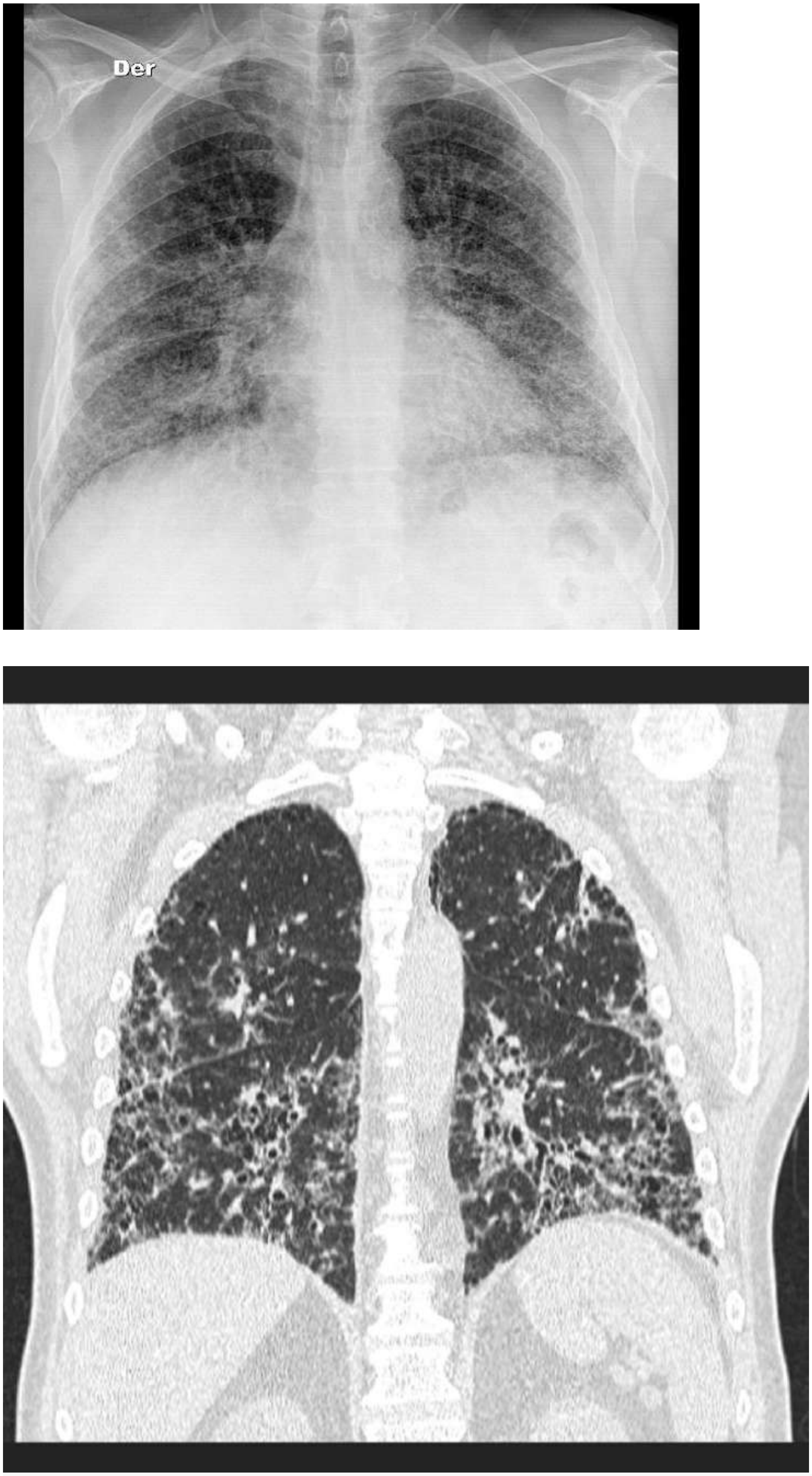
- pulmonary rehabilitation
- very few medications have been shown to give any benefit in IPF. There is some evidence that pirfenidone (an antifibrotic agent) may be useful in selected patients (see NICE guidelines)
- many patients will require supplementary oxygen and eventually a lung transplant

Prognosis

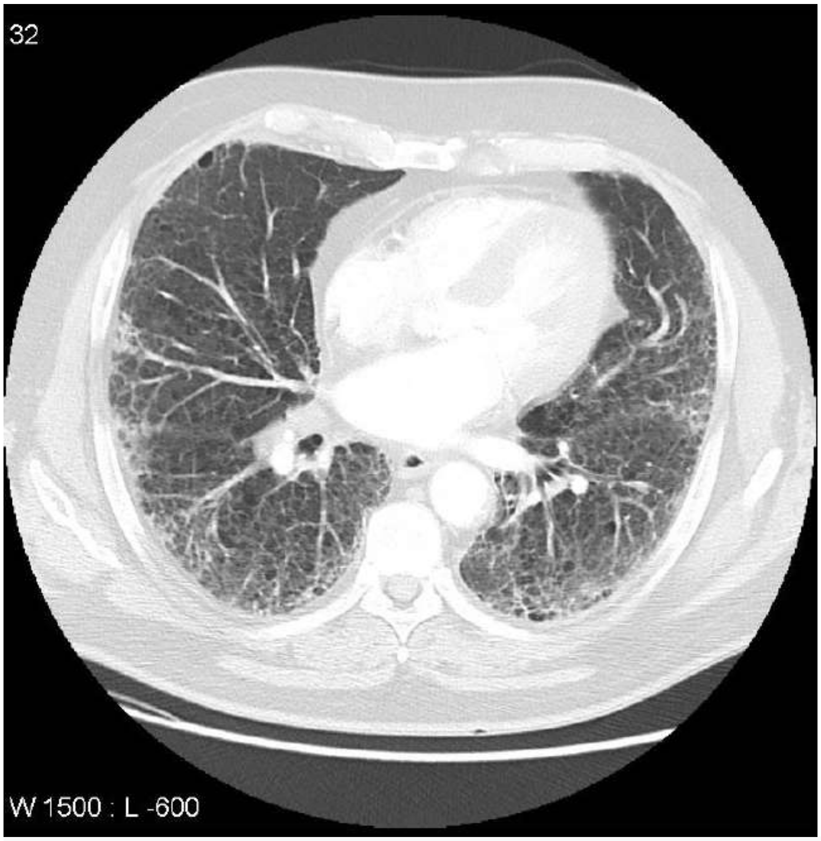
- poor, average life expectancy is around 3-4 years



Chest X-ray shows sub-pleural reticular opacities that increase from the apex to the bases of the lungs



Chest X-ray and CT scan from a patient who presented with dyspnoea. The x-ray shows reitcular opacities predominantly in the bases. In addition the CT demonstrates honeycombing and traction bronchiectasis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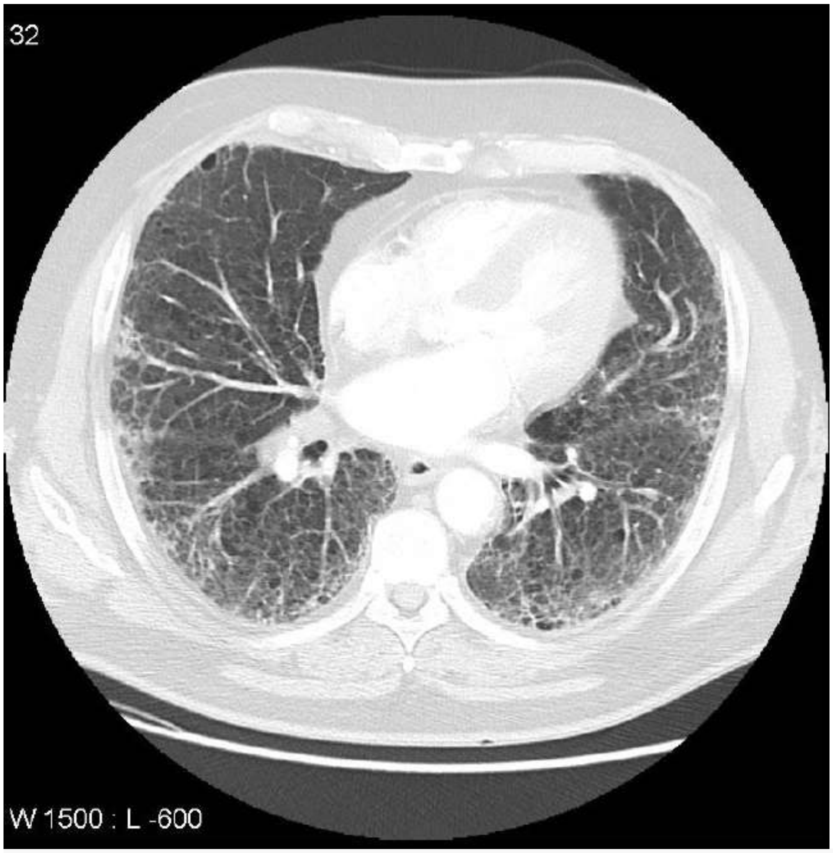
CT scan showing advanced pulmonary fibrosis including 'honeycombing'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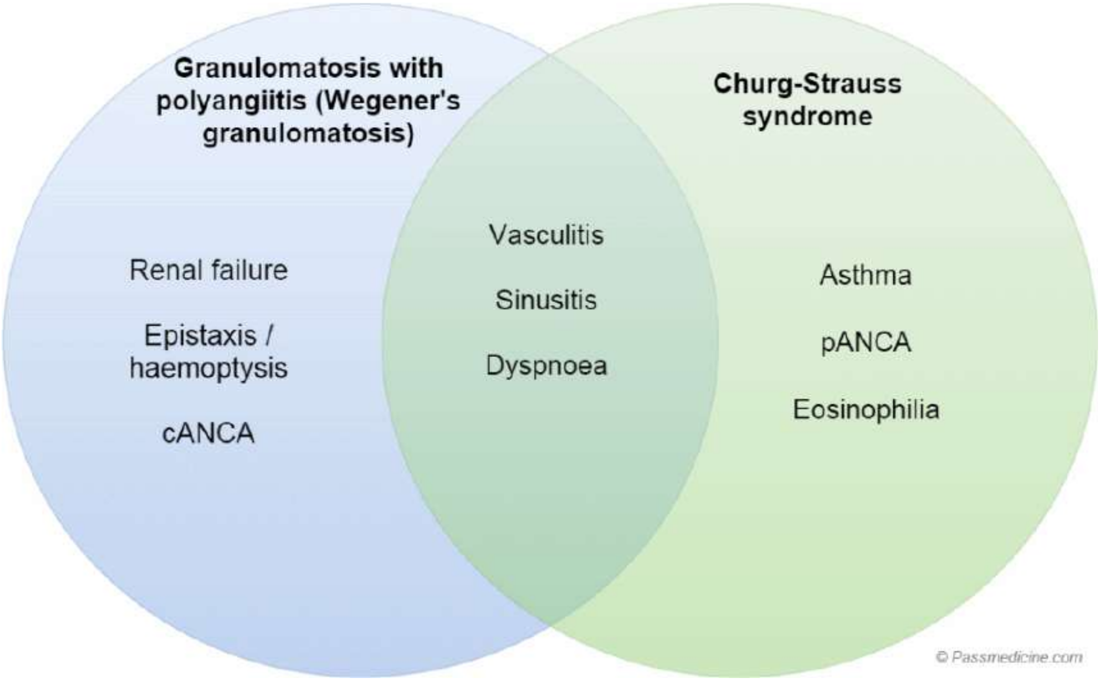
CT scan showing advanced pulmonary fibrosis including 'honeycombing'

# EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (CHURG-STRAUSS SYNDROME)

Eosinophilic granulomatosis with polyangiitis (EGPA) is now the preferred term for Churg-Strauss syndrome. It is an ANCA associated small-medium vessel vasculitis.

Features
- asthma
- blood eosinophilia (e.g. > 10%)
- paranasal sinusitis
- mononeuritis multiplex
- pANCA positive in 60%


Granulomatosis with polyangiitis (Wegener's granulomatosis)
Churg-Strauss syndrome
Renal failure
Epistaxis / haemoptysis
cANCA
Vasculitis
Sinusitis
Dyspnoea
Asthma
pANCA
Eosinophilia
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Comparison of granulomatosis with polyangiitis and Churg-Strauss syndrome

Leukotriene receptor antagonists may precipitate the disease.

# GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S GRANULOMATOSIS)

Granulomatosis with polyangiitis is now the preferred term for Wegener's granulomatosis. It is an autoimmune condition associated with a necrotizing granulomatous vasculitis, affecting both the upper and lower respiratory tract as well as the kidneys.

Features

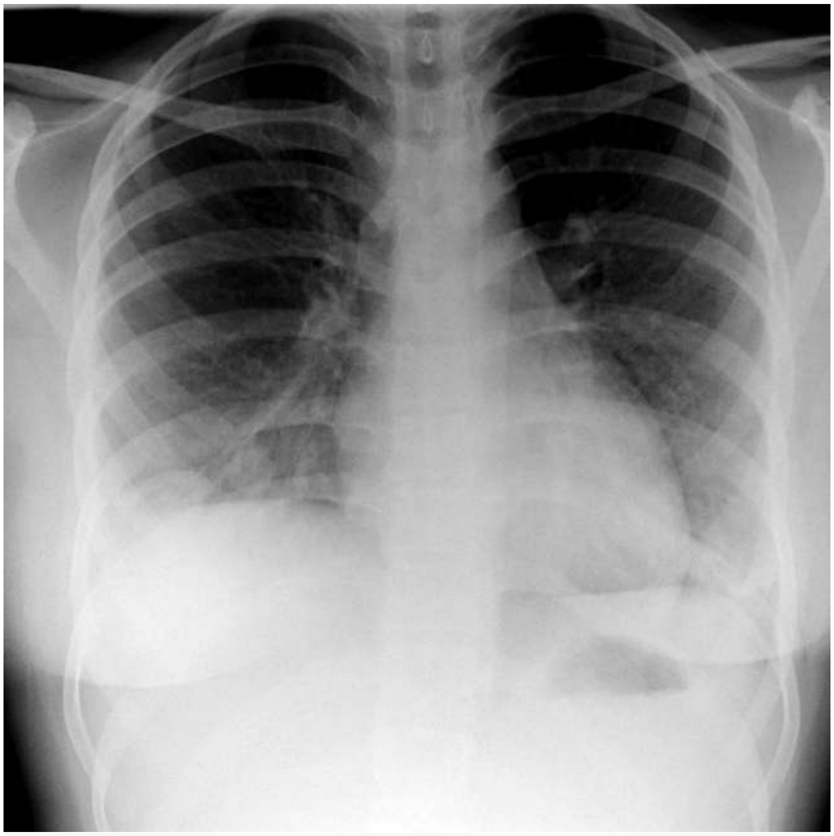
- upper respiratory tract: epistaxis, sinusitis, nasal crusting
- lower respiratory tract: dyspnoea, haemoptysis
- rapidly progressive glomerulonephritis ('pauci-immune', 80% of patients)
- saddle-shape nose deformity
- also: vasculitic rash, eye involvement (e.g. proptosis), cranial nerve lesions

Investigations

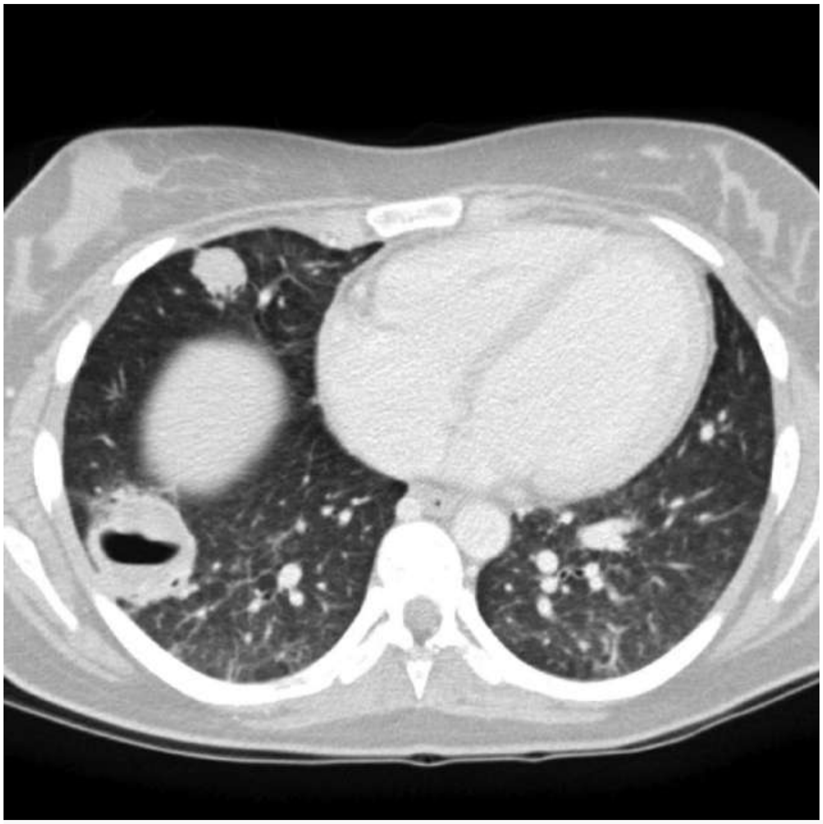
- cANCA positive in > 90%, pANCA positive in 25%
- chest x-ray: wide variety of presentations, including cavitating lesions
- renal biopsy: epithelial crescents in Bowman's capsule

Management

- steroids
- cyclophosphamide (90% response)
- plasma exchange
- median survival = 8-9 years



Chest x-ray from a young patient with granulomatosis with polyangiitis. Whilst the changes are subtle it demonstrates a number of ill-defined nodules the largest of which projects over the dome of the right hemidiaphragm. This nodule appears to have a central lucency suggesting cavitation



CT of the same patient showing the changes in a much more obvious way, confirming the presence of at least 2 nodules, the larger of the two having a large central cavity and and air-fluid level

## MICROSCOPIC POLYANGIITIS

Microscopic polyangiitis is a small-vessel ANCA vasculitis.

Features

- renal impairment: raised creatinine, haematuria, proteinuria
- fever
- other systemic symptoms: lethargy, myalgia, weight loss
- rash: palpable purpura
- cough, dyspnoea, haemoptysis
- mononeuritis multiplex

Investigations

- pANCA (against MPO) - positive in 50-75%
- cANCA (against PR3) - positive in 40%

# PULMONARY EOSINOPHILIA

Pulmonary eosinophilia describes a situation where there are increased numbers of eosinophils in the lung airways and parenchyma. This is generally associated with a blood eosinophilia.

Causes of pulmonary eosinophilia
- Churg-Strauss syndrome
- allergic bronchopulmonary aspergillosis (ABPA)
- Loffler's syndrome
- eosinophilic pneumonia
- hypereosinophilic syndrome
- tropical pulmonary eosinophilia
- drugs: nitrofurantoin, sulphonamides
- less common: Wegener's granulomatosis

Loffler's syndrome
- transient CXR shadowing and blood eosinophilia
- thought to be due to parasites such as Ascaris lumbricoides causing an alveolar reaction
- presents with a fever, cough and night sweats which often last for less than 2 weeks.
- generally a self-limiting disease

Acute eosinophilic pneumonia
- highly responsive to steroids

Tropical pulmonary eosinophilia
- associated with Wuchereria bancrofti infection

# EXTRINSIC ALLERGIC ALVEOLITIS

Extrinsic allergic alveolitis (EAA, also known as hypersensitivity pneumonitis) is a condition caused by hypersensitivity induced lung damage due to a variety of inhaled organic particles. It is thought to be largely caused by immune-complex mediated tissue damage (type III hypersensitivity) although delayed hypersensitivity (type IV) is also thought to play a role in EAA, especially in the chronic phase.

Examples
- bird fanciers' lung: avian proteins
- farmers lung: spores of Saccharopolyspora rectivirgula (formerly Micropolyspora faeni)
- malt workers' lung: Aspergillus clavatus
- mushroom workers' lung: thermophilic actinomycetes*

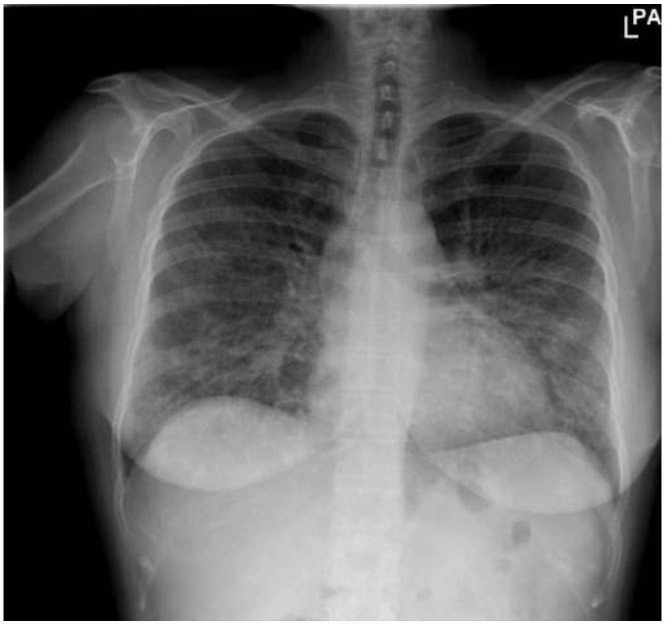
Presentation

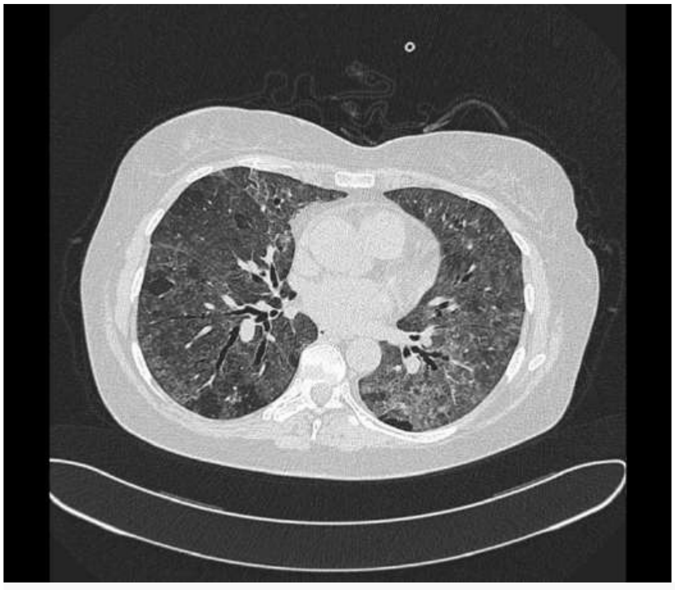
- acute: occur 4-8 hrs after exposure, SOB, dry cough, fever
- chronic

Investigation

- chest x-ray: upper/mid-zone fibrosis
- bronchoalveolar lavage: lymphocytosis
- blood: NO eosinophilia

*here the terminology is slightly confusing as thermophilic actinomycetes is an umbrella term covering strains such as Micropolyspora faeni





Chest x-ray and CT scan from a middle-aged woman who presented with dyspnoea. The CT demonstrates multuple centrilobular ground glass nodules consistent with hypersensitivity pneumonitis

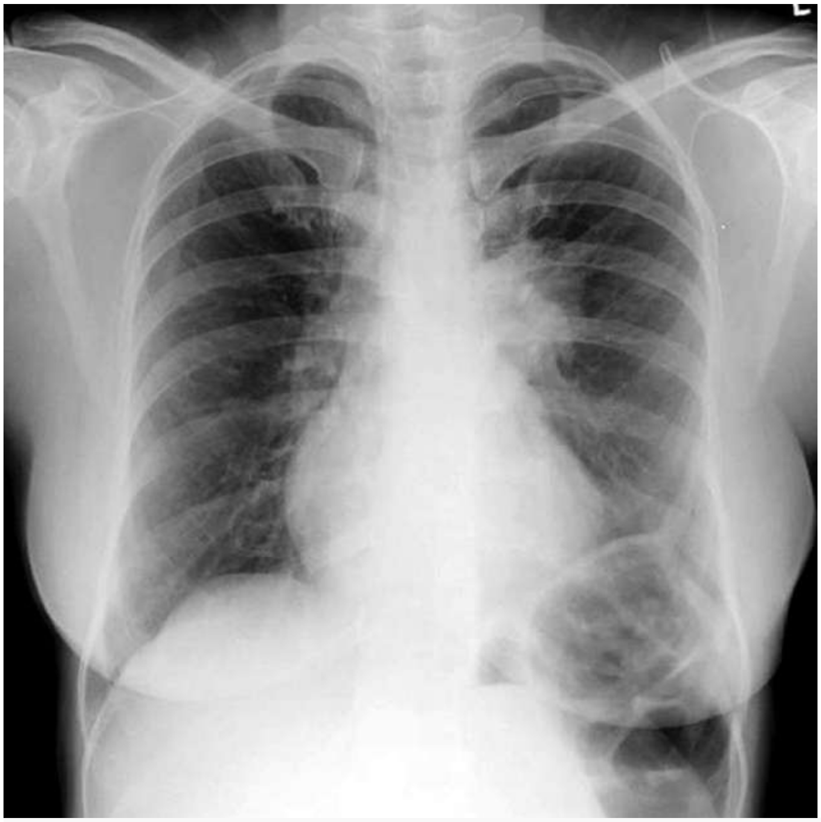
# ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

Allergic bronchopulmonary aspergillosis results from an allergy to Aspergillus spores. In the exam questions often give a history of bronchiectasis and eosinophilia.

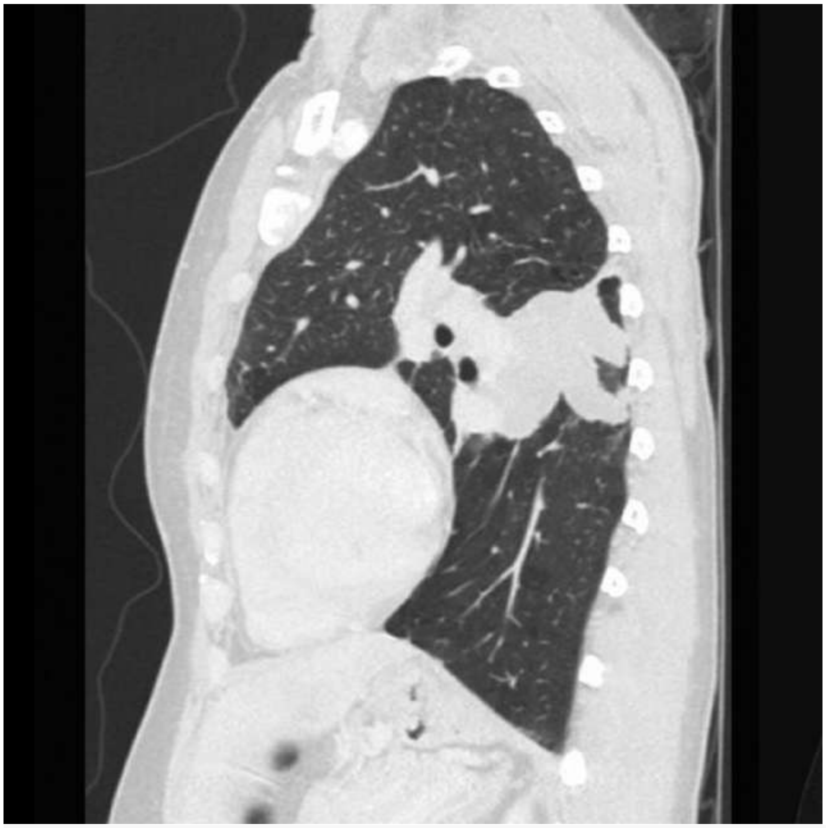
Features
- bronchoconstriction: wheeze, cough, dyspnoea. Patients may have a previous label of asthma
- bronchiectasis (proximal)

Investigations
- eosinophilia
- flitting CXR changes
- positive radioallergosorbent (RAST) test to Aspergillus
- positive IgG precipitins (not as positive as in aspergilloma)
- raised IgE

Management
- steroids
- itraconazole is sometimes introduced as a second-line agent



Chest x-ray of a 40-year-old woman with ABPA demonstrating a mass overlying the left hilum. In the right upper parahilar region a few ring shadow / tram track opacities are also noted, suggestive of bronchiectasis



CT scan from the same patient. CT reveals a branching lesion in the superior segment of the left lower lobe with classic finger in glove appearance which represents of mucous filling dilated bronchi (i.e. bronchocoeles). Bronchocoeles are a common feature of allergic bronchopulmonary aspergillosis (ABPA)

# ALTITUDE RELATED DISORDERS

There are three main types of altitude related disorders: acute mountain sickness (AMS), which may progress to high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE). All three conditions are due to the chronic hypobaric hypoxia which develops at high altitudes

Acute mountain sickness is generally a self-limiting condition. Features of AMS start to occur above 2,500 - 3,000m, developing gradually over 6-12 hours and potentially last a number of days:
- headache
- nausea
- fatigue

Prevention and treatment of AMS
- the risk of AMS may actually be positively correlated to physical fitness
- gain altitude at no more than 500 m per day
- acetazolamide (a carbonic anhydrase inhibitor) is widely used to prevent AMS and has a supporting evidence base
- treatment: descent

A minority of people above 4,000m go onto develop high altitude pulmonary oedema (HAPE) or high altitude cerebral oedema (HACE), potentially fatal conditions
- HAPE presents with classical pulmonary oedema features
- HACE presents with headache, ataxia, papilloedema

Management of HACE
- descent
- dexamethasone

Management of HAPE
- descent
- nifedipine, dexamethasone, acetazolamide, phosphodiesterase type V inhibitors*
- oxygen if available

*the relative merits of these different treatments has only been studied in small trials. All seem to work by reducing systolic pulmonary artery pressure

# DRUGS USED IN RESPIRATORY MEDICINE

| Drug | Mechanism of action | Notes |
|---|---|---|
| Salbutamol | Beta receptor agonist | • Short-acting inhaled bronchodilator. Relaxes bronchial smooth muscle through effects on beta 2 receptors<br>• Used in asthma and chronic obstructive pulmonary disease (COPD).<br>• Salmeterol has similar effects but is long-acting |
| Corticosteroids | Anti-inflammatory | • Inhaled corticosteroids are used as mainterance therapy<br>• Oral or intravenous corticosteroids are used following an acute exacerbation of asthma or COPD |
| Ipratropium | Blocks the muscarinic acetylcholine receptors | • Short-acting inhaled bronchodilator. Relaxes bronchial smooth muscle<br>• Used primarily in COPD<br>• Tiotropium has similar effects but is long-acting |
| Methylxanthines (e.g. theophylline) | Non-specific inhibitor of phosphodiesterase resulting in an increase in cAMP | • Given orally or intravenously<br>• Has a narrow therapeutic index |
| Monteleukast, zafirlukast | Blocks leukotriene receptors | • Usually taken orally<br>• Useful in aspirin-induced asthma |

# PASSMEDICINE NOTES GASTROENTEROLOGY

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# GASTROINTESTINAL PHYSIOLOGY: ENZYMES

Amylase is present in saliva and pancreatic secretions. It breaks starch down into sugar

The following brush border enzymes are involved in the breakdown of carbohydrates:
- maltase: cleaves disaccharide maltose to glucose + glucose
- sucrase: cleaves sucrose to fructose and glucose
- lactase: cleaves disaccharide lactose to glucose + galactose

# FOOD ENERGY

The amount of energy a food product contains is expressed in calories (kcal).

In simple terms, per unit weight, fats contain twice as many calories as protein or carbohydrates.

# ENERGY FROM FOOD

The amount of energy that may be derived from 1 gram of food is as follows:
carbohydrates: 4 kcal
protein: 4 kcal
fat: 9 kcal

# ENTERAL FEEDING

Key points
- Identify patients as malnourished or at risk (see below)
- Identify unsafe or inadequate oral intake with functional GI tract
- Consider for enteral feeding
- Gastric feeding unless upper GI dysfunction (then for duodenal or jejunal tube)
- Check NG placement using aspiration and pH (check post pyloric tubes with AXR)
- Gastric feeding > 4 weeks consider long-term gastrostomy
- Consider bolus or continuous feeding into the stomach
- ITU patients should have continuous feeding for 16-24h (24h if on insulin)
- Consider motility agent in ITU or acute patients for delayed gastric emptying. If this doesn't work then try post pyloric feeding or parenteral feeding.
- PEG can be used 4 hours after insertion, but should not be removed until >2 weeks after insertion.

Surgical patients due to have major abdominal surgery: if malnourished, unsafe swallow/inadequate oral intake and functional GI tract then consider pre operative enteral feeding.

**Patients identified as being malnourished**
- BMI < 18.5 kg/m2
- unintentional weight loss of > 10% over 3-6/12
- BMI < 20 kg/m2 and unintentional weight loss of > 5% over 3-6/12

**AT RISK of malnutrition**
- Eaten nothing or little > 5 days, who are likely to eat little for a further 5 days
- Poor absorptive capacity
- High nutrient losses
- High metabolism

**Reference**

Stroud M et al. Guidelines for enteral feeding in adult hospital patients. Gut 2003; 52(Suppl VII):vii1 - vii12.

# TOTAL PARENTERAL NUTRITION

- Commonly used in nutritionally compromised surgical patients
- Bags contain combinations of glucose, lipids and essential electrolytes, the exact composition is determined by the patients nutritional requirements.
- Although it may be infused peripherally, this may result in thrombophlebitis.
- Longer term infusions should be administered into a central vein (preferably via a PICC line).
- Complications are related to sepsis, re-feeding syndromes and hepatic dysfunction.

# FERRITIN

Ferritin is an intracellular protein that binds iron and stores it to be released in a controlled fashion at sites where iron is required.

**Increased ferritin levels**

This is typically defined as > 300 µg/L in men/postmenopausal women and > 200 µµg/L in premenopausal women.

Ferritin is an acute phase protein and may be synthesised in increased quantities in situations where inflammatory activity is ongoing. Falsely elevated results may therefore be encountered clinically and need to be taken in the context of the clinical picture and blood results.

We can split the causes of increased ferritin levels into 2 distinct categories;

| Without iron overload (around 90% of patients) | With iron overload (around 10% of patients) |
|---|---|
| Inflammation (due to ferritin being an acute phase reactant)<br>Alcohol excess<br>Liver disease<br>Chronic kidney disease<br>Malignancy | Primary iron overload (hereditary haemochromatosis)<br><br>Secondary iron overload (e.g. following repeated transfusions) |

The best test to see whether iron overload is present is **transferrin saturation**. Typically, normal values of < 45% in females and < 50% in males exclude iron overload.

**Reduced ferritin levels**

Because iron and ferritin are bound the total body ferritin levels may be decreased in cases of iron deficiency anaemia.

Measurement of serum ferritin levels can be useful in determining whether an apparently low haemoglobin and microcytosis is truly caused by an iron deficiency state.

# DYSPHAGIA

The table below gives characteristic exam question features for conditions causing dysphagia. Remember that new-onset dysphagia is a red flag symptom that requires urgent endoscopy, regardless of age or other symptoms.

| Causes | Notes |
|---|---|
| **Oesophageal cancer** | Dysphagia may be associated with weight loss, anorexia or vomiting during eating<br>Past history may include Barrett's oesophagus, GORD, excessive smoking or alcohol use |
| **Oesophagitis** | There may be a history of heartburn<br>Odynophagia but no weight loss and systemically well |
| **Oesophageal candidiasis** | There may be a history of HIV or other risk factors such as steroid inhaler use |
| **Achalasia** | Dysphagia of both liquids and solids from the start<br>Heartburn<br>Regurgitation of food - may lead to cough, aspiration pneumonia etc |
| **Pharyngeal pouch** | More common in older men<br>Represents a posteromedial herniation between thyropharyngeus and cricopharyngeus muscles<br>Usually not seen but if large then a midline lump in the neck that gurgles on palpation<br>Typical symptoms are dysphagia, regurgitation, aspiration and chronic cough. Halitosis may occasionally be seen |

| Causes | Notes |
|---|---|
| **Systemic sclerosis** | Other features of CREST syndrome may be present, namely Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia<br>As well as oesophageal dysmotility the lower oesophageal sphincter (LES) pressure is decreased. This contrasts to achalasia where the LES pressure is increased |
| **Myasthenia gravis** | Other symptoms may include extraocular muscle weakness or ptosis<br>Dysphagia with liquids as well as solids |
| **Globus hystericus** | There may be a history of anxiety<br>Symptoms are often intermittent and relieved by swallowing<br>Usually painless - the presence of pain should warrant further investigation for organic causes |

**Causes of dysphagia - by classification**

As with many conditions, it's often useful to think about causes of a symptom in a structured way:

| Classification | Examples |
|---|---|
| **Extrinsic** | • Mediastinal masses<br>• Cervical spondylosis |
| **Oesophageal wall** | • Achalasia<br>• Diffuse oesophageal spasm<br>• Hypertensive lower oesophageal sphincter |
| **Intrinsic** | • Tumours<br>• Strictures<br>• Oesophageal web<br>• Schatzki rings |
| **Neurological** | • CVA<br>• Parkinson's disease<br>• Multiple Sclerosis<br>• Brainstem pathology<br>• Myasthenia Gravis |

**Investigation**

All patients require an upper GI endoscopy unless there are compelling reasons for this not to be performed. Motility disorders may be best appreciated by undertaking fluoroscopic swallowing studies.

A full blood count should be performed.

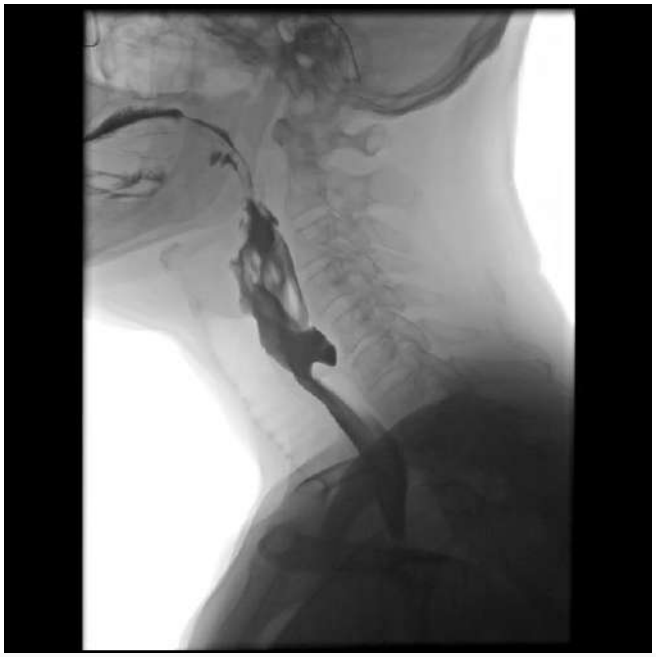
Ambulatory oesophageal pH and manometry studies will be required to evaluate conditions such as achalasia and patients with GORD being considered for fundoplication surgery.

# PHARYNGEAL POUCH

A pharyngeal pouch is a posteromedial diverticulum through Killian's dehiscence. Killian's dehiscence is a triangular area in the wall of the pharynx between the thyropharyngeus and cricopharyngeus muscles. It is more common in older patients and is 5 times more common in men

Features
- dysphagia
- regurgitation
- aspiration
- neck swelling which gurgles on palpation
- halitosis

Management
- surgery



Still image taken from a barium swallow with fluoroscopy. During swallowing an outpouching of the posterior hypopharyngeal wall is visualised at the level C5-C6, right above the upper oesophageal sphincter

# BARRETT'S OESOPHAGUS

Barrett's refers to the metaplasia of the lower oesophageal mucosa, with the usual squamous epithelium being replaced by columnar epithelium. There is an increased risk of oesophageal adenocarcinoma, estimated at 50-100 fold. There are no screening programs for Barrett's - it's typically identified when patients have an endoscopy for evaluation of upper gastrointestinal symptoms such as dyspepsia.

Barrett's can be subdivided into short (<3cm) and long (>3cm). The length of the affected segment correlates strongly with the chances of identifying metaplasia. The overall prevalence of Barrett's oesophagus is difficult to determine but may be in the region of 1 in 20 and is identified in up to 12% of those undergoing endoscopy for reflux.

Histological features
- the columnar epithelium may resemble that of either the cardiac region of the stomach or that of the small intestine (e.g. with goblet cells, brush border)

Risk factors
- gastro-oesophageal reflux disease (GORD) is the single strongest risk factor
- male gender (7:1 ratio)
- smoking
- central obesity

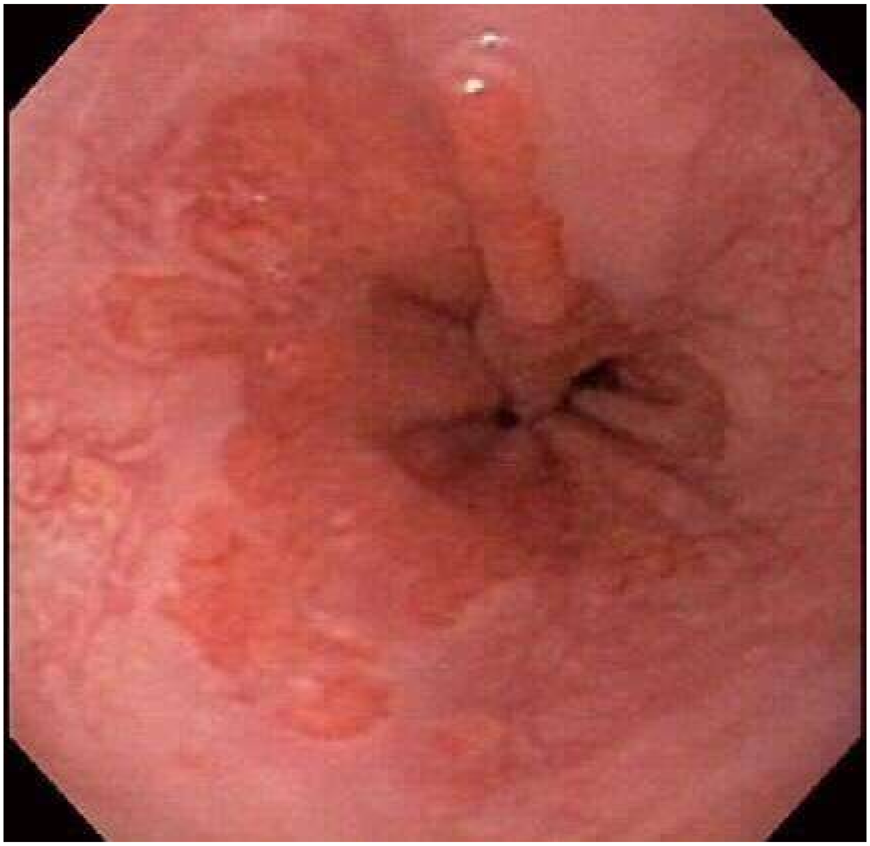
Interestingly alcohol does not seem to be an independent risk factor for Barrett's although it is associated with both GORD and oesophageal cancer.

Whilst Barrett's oesophagus itself is asymptomatic clearly patients will often have coexistent GORD symptoms.

Management
- endoscopic surveillance with biopsies
- high-dose proton pump inhibitor: whilst this is commonly used in patients with Barrett's the evidence base that this reduces the change of progression to dysplasia or induces regression of the lesion is limited

Endoscopic surveillance
- for patients with metaplasia (but not dysplasia) endoscopy is recommended every 3-5 years

If dysplasia of any grade is identified endoscopic intervention is offered. Options include:
- endoscopic mucosal resection
- radiofrequency ablation



Endoscopy image showing a short segment of Barrett's oesophagus

# ACHALASIA

Failure of oesophageal peristalsis and of relaxation of lower oesophageal sphincter (LOS) due to degenerative loss of ganglia from Auerbach's plexus i.e. LOS contracted, oesophagus above dilated. Achalasia typically presents in middle-age and is equally common in men and women.

Clinical features

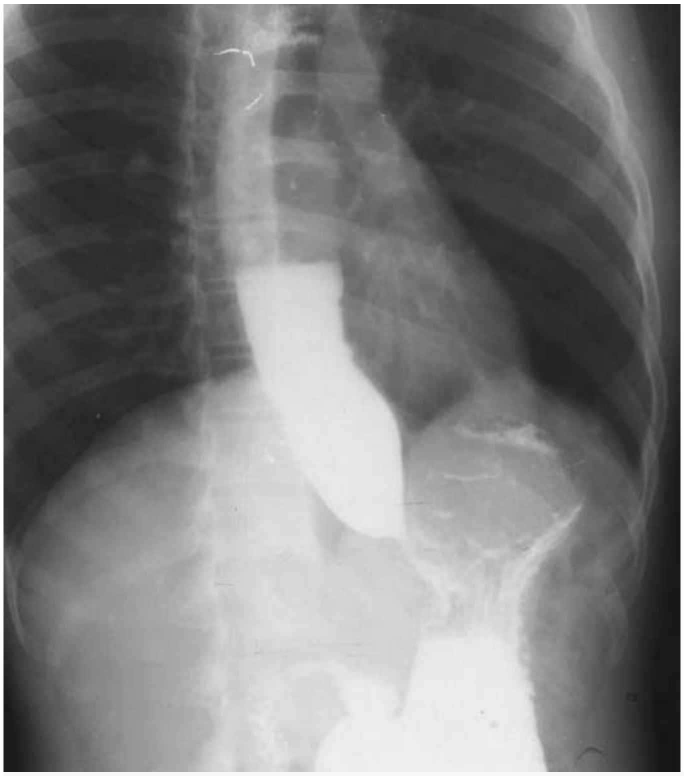
- dysphagia of BOTH liquids and solids
- typically variation in severity of symptoms
- heartburn
- regurgitation of food - may lead to cough, aspiration pneumonia etc
- malignant change in small number of patients

Investigations

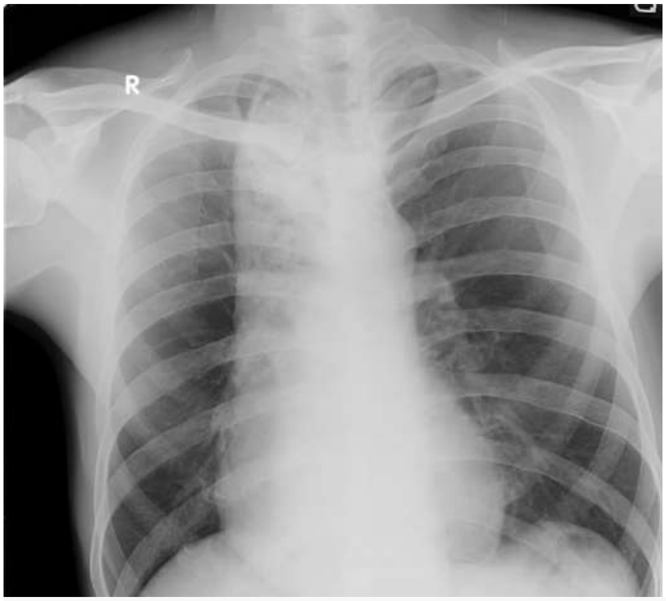
- oesophageal manometry: excessive LOS tone which doesn't relax on swallowing - considered most important diagnostic test
- barium swallow shows grossly expanded oesophagus, fluid level, 'bird's beak' appearance
- CXR: wide mediastinum, fluid level

Treatment

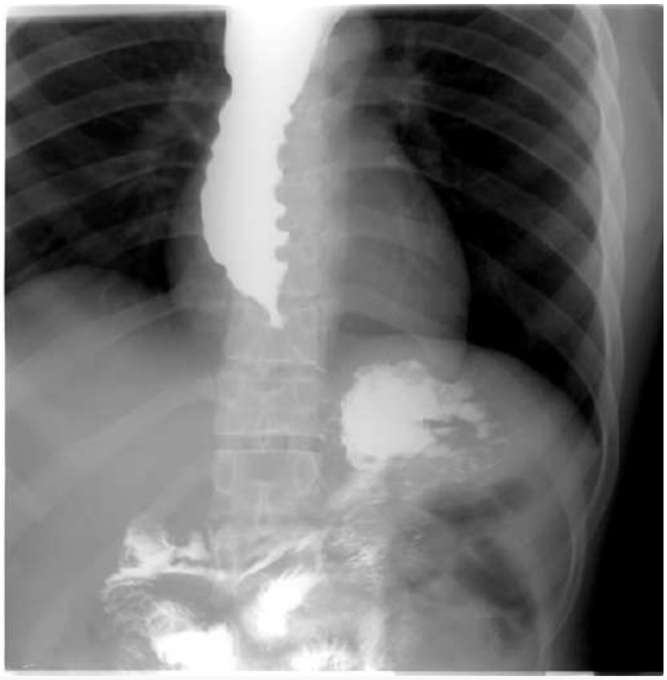
- intra-sphincteric injection of botulinum toxin
- Heller cardiomyotomy
- pneumatic (balloon) dilation
- drug therapy has a role but is limited by side-effects



This film demonstrates the classical 'bird's beak' appearance of the lower oesophagus that is seen in achalasia. An air-fluid level is also seen due to a lack of peristalsis



Mediastinal widening secondary to achalasia. An air-fluid level can sometimes be seen on CXR but it is not visible on this film



Barium swallow - grossly dilated filled oesophagus with a tight stricture at the gastroesophageal junction resulting in a 'bird's beak' appearance. Tertiary contractions give rise to a corkscrew appearance of the oesophagus

# OESOPHAGEAL CANCER

Until recent times oesophageal cancer was most commonly due to a squamous cell carcinoma but the incidence of adenocarcinoma is rising rapidly. Adenocarcinoma is now the most common type of oesophageal cancer and is more likely to develop in patients with a history of gastro-oesophageal reflux disease (GORD) or Barrett's.

The majority of adenocarcinomas are located near the gastroesophageal junction whereas squamous cell tumours are most commonly found in the middle third of the oesophagus.

Risk factors
- smoking
- alcohol
- GORD
- Barrett's oesophagus
- achalasia
- Plummer-Vinson syndrome
- squamous cell carcinoma is also linked to diets rich in nitrosamines
- rare: coeliac disease, scleroderma

Features
- dysphagia: the most common presenting symptom
- anorexia and weight loss
- vomiting

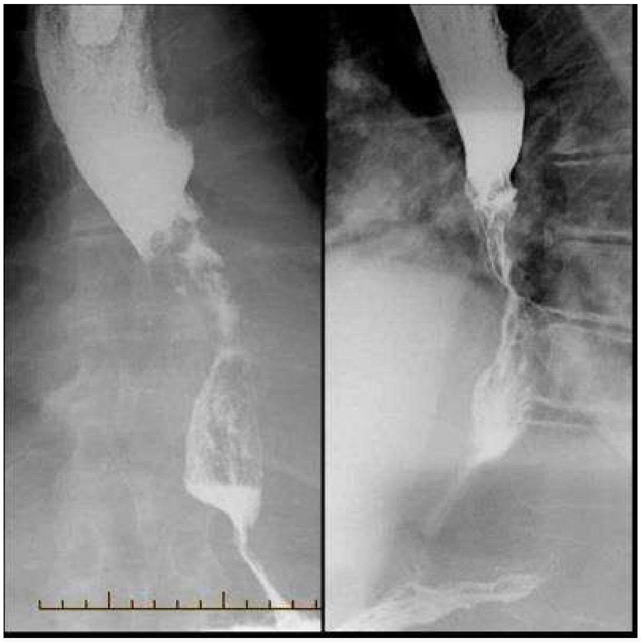
- other possible features include: odynophagia, hoarseness, melaena, cough

Diagnosis

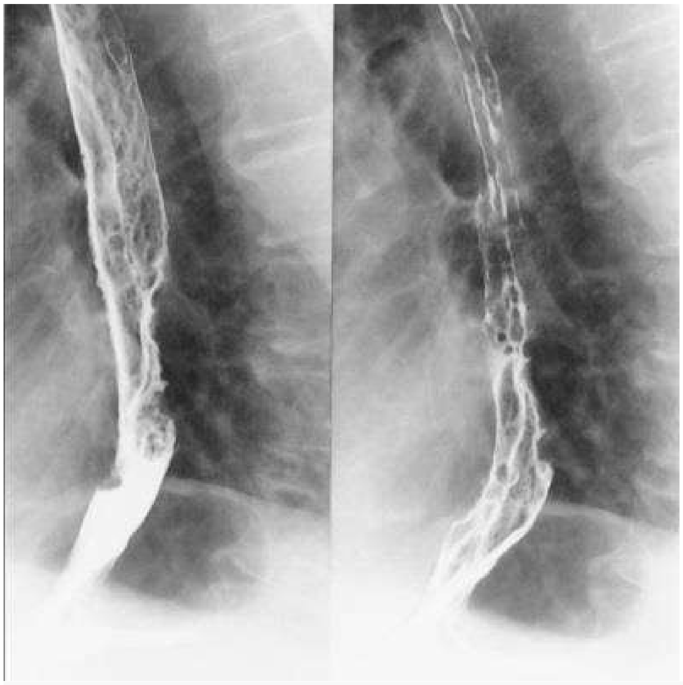
- Upper GI endoscopy is the first line test
- Contrast swallow may be of benefit in classifying benign motility disorders but has no place in the assessment of tumours
- Staging is initially undertaken with CT scanning of the chest, abdomen and pelvis. If overt metastatic disease is identified using this modality then further complex imaging is unnecessary
- If CT does not show metastatic disease, then local stage may be more accurately assessed by use of endoscopic ultrasound
- Staging laparoscopy is performed to detect occult peritoneal disease. PET CT is performed in those with negative laparoscopy. Thoracoscopy is not routinely performed.

Treatment

- Operable disease is best managed by surgical resection.
- The most standard procedure is an Ivor- Lewis type oesophagectomy. This procedure involves the mobilisation of the stomach and division of the oesophageal hiatus. The abdomen is closed and a right sided thoracotomy performed. The stomach is brought into the chest and the oesophagus mobilised further. An intrathoracic oesophagogastric anastomosis is constructed. Alternative surgical strategies include a transhiatal resection (for distal lesions), a left thoraco-abdominal resection (difficult access due to thoracic aorta) and a total oesophagectomy (McKeown) with a cervical oesophagogastric anastomosis.
- The biggest surgical challenge is that of anastomotic leak, with an intrathoracic anastomosis this will result in mediastinitis. With high mortality. The McKeown technique has an intrinsically lower systemic insult in the event of anastomotic leakage.
- In addition to surgical resection many patients will be treated with adjuvant chemotherapy.



Barium swallow - 5cm irregular narrowing of the mid-thoracic oesophagus with proximal shouldering



Fluoroscopy - a region of fixed, irregular stricturing is seen in the distal oesophagus

# OESOPHAGEAL DISORDERS

The table below lists a small group of less common oesophageal disorders.

| Disorder | Notes |
|---|---|
| Plummer-Vinson syndrome | Triad of:<br>• dysphagia (secondary to oesophageal webs)<br>• glossitis<br>• iron-deficiency anaemia<br>Treatment includes iron supplementation and dilation of the webs |
| Mallory-Weiss syndrome | Severe vomiting → painful mucosal lacerations at the gastroesophageal junction resulting in haematemesis. Common in alcoholics |
| Boerhaave syndrome | Severe vomiting → oesophageal rupture |

# DRUGS CAUSING DYSPEPSIA

Causes

- NSAIDs
- bisphosphonates
- steroids

The following drugs may cause reflux by reducing lower oesophageal sphincter (LOS) pressure

- calcium channel blockers*
- nitrates*
- theophyllines

*calcium channel blockers and nitrates are occasionally used in the management of achalasia, itself a cause of dyspepsia, because of their effect on the LOS.

# GASTRO-OESOPHAGEAL REFLUX DISEASE: INVESTIGATION

Overview

- poor correlation between symptoms and endoscopy appearance

Indications for upper GI endoscopy:

- age > 55 years
- symptoms > 4 weeks or persistent symptoms despite treatment
- dysphagia
- relapsing symptoms
- weight loss

If endoscopy is negative consider 24-hr oesophageal pH monitoring (the gold standard test for diagnosis)

| Disorder | Notes |
|---|---|
| Plummer-Vinson syndrome | Triad of:<br>• dysphagia (secondary to oesophageal webs)<br>• glossitis<br>• iron-deficiency anaemia<br>Treatment includes iron supplementation and dilation of the webs |
| Mallory-Weiss syndrome | Severe vomiting → painful mucosal lacerations at the gastroesophageal junction resulting in haematemesis. Common in alcoholics |
| Boerhaave syndrome | Severe vomiting → oesophageal rupture |

# HELICOBACTER PYLORI

Helicobacter pylori is a Gram negative bacteria associated with a variety of gastrointestinal problems, principally peptic ulcer disease

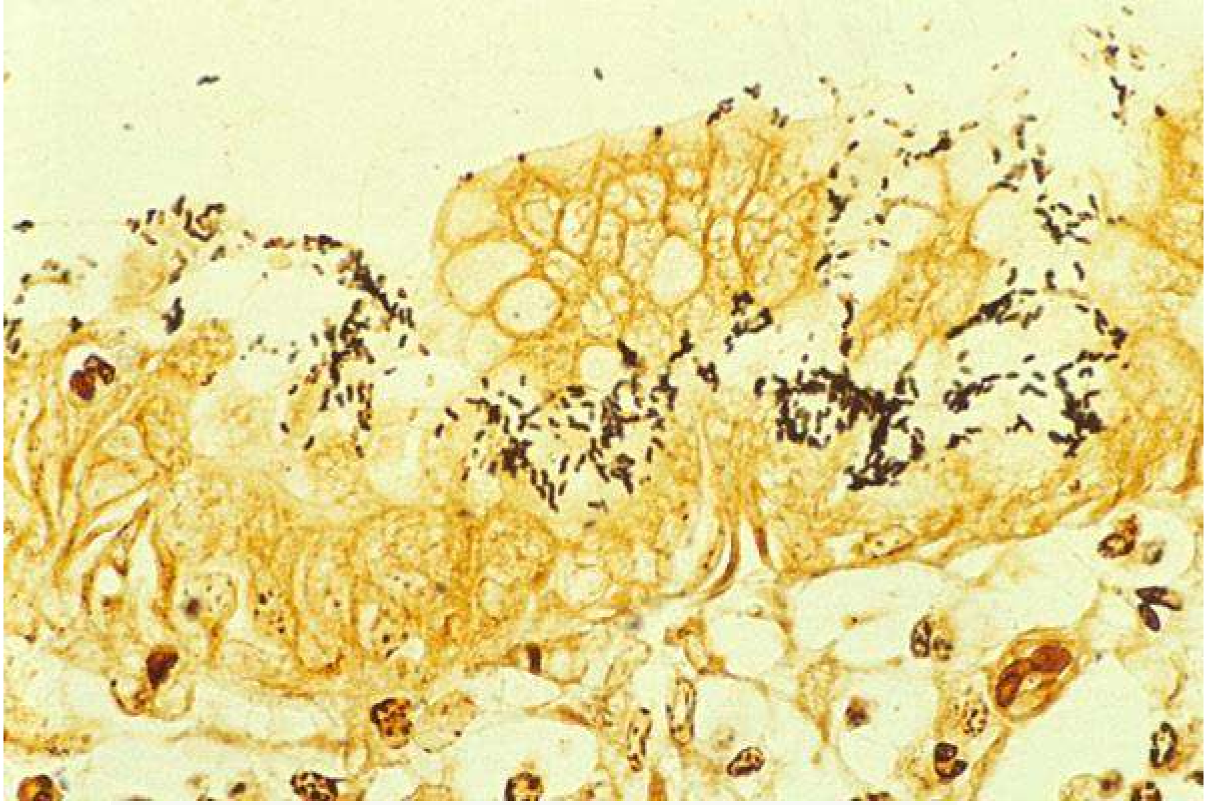
Associations

- peptic ulcer disease (95% of duodenal ulcers, 75% of gastric ulcers)
- gastric cancer
- B cell lymphoma of MALT tissue (eradication of H pylori results causes regression in 80% of patients)
- atrophic gastritis

The role of H pylori in Gastro-oesophageal reflux disease (GORD) is unclear - there is currently no role in GORD for the eradication of H pylori

Management - eradication may be achieved with a 7 day course of

- a proton pump inhibitor + amoxicillin + clarithromycin, or
- a proton pump inhibitor + metronidazole + clarithromycin



*H. pylori* colonized on the surface of regenerative epithelium (silver stain)

## HELICOBACTER PYLORI: TESTS

Urea breath test

- patients consume a drink containing carbon isotope 13 (13C) enriched urea
- urea is broken down by H. pylori urease
- after 30 mins patient exhale into a glass tube
- mass spectrometry analysis calculates the amount of 13C CO2
- should not be performed within 4 weeks of treatment with an antibacterial or within 2 weeks of an antisecretory drug (e.g. a proton pump inhibitor)
- sensitivity 95-98%, specificity 97-98%
- may be used to check for H. pylori eradication

Rapid urease test (e.g. CLO test)

- biopsy sample is mixed with urea and pH indicator
- colour change if H pylori urease activity
- sensitivity 90-95%, specificity 95-98%

Serum antibody

- remains positive after eradication
- sensitivity 85%, specificity 80%

Culture of gastric biopsy

- provide information on antibiotic sensitivity
- sensitivity 70%, specificity 100%

Gastric biopsy

- histological evaluation alone, no culture
- sensitivity 95-99%, specificity 95-99%

Stool antigen test

- sensitivity 90%, specificity 95%

# PROTON PUMP INHIBITORS

Proton pump inhibitors (PPI) cause irreversible blockade of H+/K+ ATPase of the gastric parietal cell.

Examples include omeprazole and lansoprazole.

Adverse effects

- hyponatraemia, hypomagnasaemia
- osteoporosis → increased risk of fractures
- microscopic colitis
- increased risk of Clostridium difficile infections

# METOCLOPRAMIDE

Metoclopramide is a D2 receptor antagonist* mainly used in the management of nausea. Other uses include:

- gastro-oesophageal reflux disease
- prokinetic action is useful in gastroparesis secondary to diabetic neuropathy
- often combined with analgesics for the treatment of migraine (migraine attacks result in gastroparesis, slowing the absorption of analgesics)

Adverse effects

- extrapyramidal effects: oculogyric crisis. This is particularly a problem in children and young adults
- hyperprolactinaemia
- tardive dyskinesia
- parkinsonism

Metoclopramide should be avoided in bowel obstruction, but may be helpful in paralytic ileus.

*whilst metoclopramide is primarily a D2 receptor antagonist, the mechanism of action is quite complicated:

- it is also a mixed 5-HT3 receptor antagonist/5-HT4 receptor agonist
- the antiemetic action is due to its antagonist activity at D2 receptors in the chemoreceptor trigger zone. At higher doses the 5-HT3 receptor antagonist also has an effect
- the gastroprokinetic activity is mediated by D2 receptor antagonist activity and 5-HT4 receptor agonist activity

# GASTRIC CANCER

There are 700,000 new cases of gastric cancer worldwide each year.

Epidemiology

- overall incidence is decreasing, but incidence of tumours arising from the cardia is increasing
- peak age = 70-80 years
- more common in Japan, China, Finland and Colombia than the West
- more common in males, 2:1

Histology

- signet ring cells may be seen in gastric cancer. They contain a large vacuole of mucin which displaces the nucleus to one side. Higher numbers of signet ring cells are associated with a worse prognosis

Associations
- H. pylori infection
- blood group A: gAstric cAncer
- gastric adenomatous polyps
- pernicious anaemia
- smoking
- diet: salty, spicy, nitrates
- may be negatively associated with duodenal ulcer

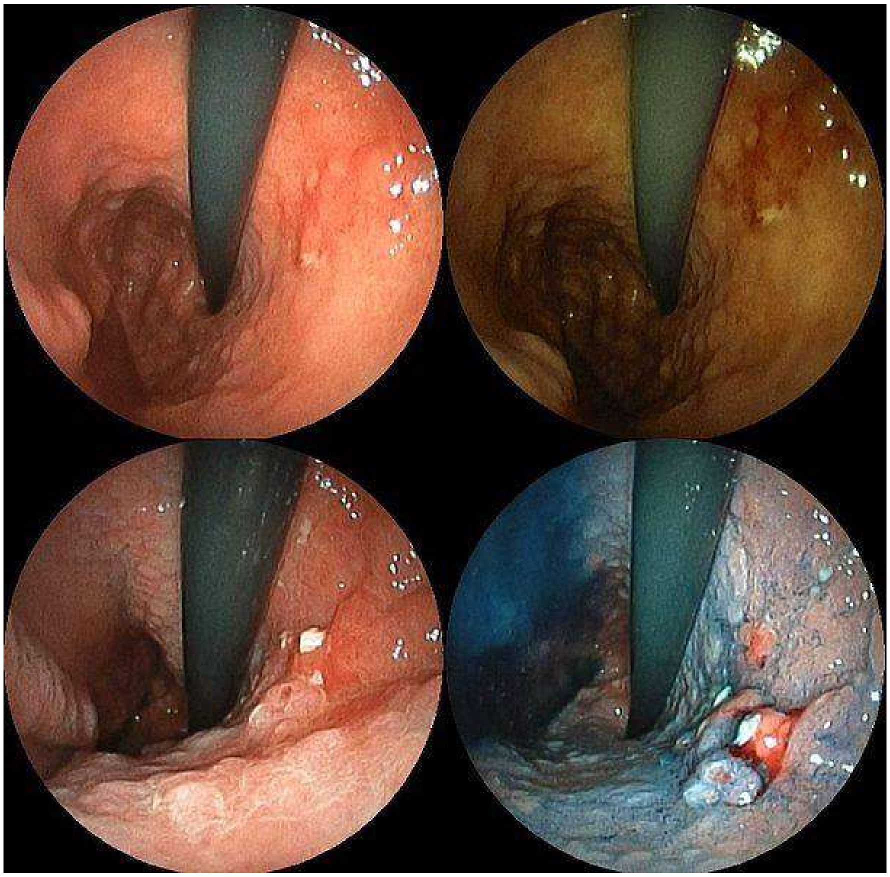
Features
- dyspepsia
- nausea and vomiting
- anorexia and weight loss
- dysphagia

Investigation
- diagnosis: endoscopy with biopsy
- staging: CT or endoscopic ultrasound - endoscopic ultrasound has recently been shown to be superior to CT

## Surgical aspects

There is some evidence of support a stepwise progression of the disease through intestinal metaplasia progressing to atrophic gastritis and subsequent dysplasia, through to cancer. The favoured staging system is TNM. The risk of lymph node involvement is related to size and depth of invasion; early cancers confined to submucosa have a 20% incidence of lymph node metastasis. Tumours of the gastro-oesophageal junction are classified as below:

| | |
|---|---|
| **Type 1** | True oesophageal cancers and may be associated with Barrett's oesophagus. |
| **Type 2** | Carcinoma of the cardia, arising from cardiac type epithelium or short segments with intestinal metaplasia at the oesophagogastric junction. |
| **Type 3** | Sub cardial cancers that spread across the junction. Involve similar nodal stations to gastric cancer. |



Upper GI endoscopy performed for dyspepsia. The addition of dye spraying (as shown in the bottom right) may facilitate identification of smaller tumours

Staging

- CT scanning of the chest abdomen and pelvis is the routine first line staging investigation in most centres.
- Laparoscopy to identify occult peritoneal disease
- PET CT (particularly for junctional tumours)

Treatment

- Proximally sited disease greater than 5-10cm from the OG junction may be treated by sub total gastrectomy
- Total gastrectomy if tumour is <5cm from OG junction
- For type 2 junctional tumours (extending into oesophagus) oesophagogastrectomy is usual
- Endoscopic sub mucosal resection may play a role in early gastric cancer confined to the mucosa and perhaps the sub mucosa (this is debated)
- Lymphadenectomy should be performed. A D2 lymphadenectomy is widely advocated by the Japanese, the survival advantages of extended lymphadenectomy have been debated. However, the overall recommendation is that a D2 nodal dissection be undertaken.
- Most patients will receive chemotherapy either pre or post operatively.

**Prognosis**

UK Data

| Disease extent | Percentage 5 year survival |
|---|---|
| All RO resections | 54% |
| Early gastric cancer | 91% |
| Stage 1 | 87% |
| Stage 2 | 65% |
| Stage 3 | 18% |

# GASTRIC MALT LYMPHOMA

Overview
- associated with H. pylori infection in 95% of cases
- good prognosis
- if low grade then 80% respond to H. pylori eradication

Features
- paraproteinaemia may be present

# PERNICIOUS ANAEMIA: INVESTIGATION

Investigation
- anti gastric parietal cell antibodies in 90% (but low specificity)
- anti intrinsic factor antibodies in 50% (specific for pernicious anaemia)
- macrocytic anaemia
- low WCC and platelets
- LDH may be raised due to ineffective erythropoiesis
- also low serum B12, hypersegmented polymorphs on film, megaloblasts in marrow
- Schilling test

Schilling test
- radiolabelled B12 given on two occasions
- first on its own
- second with oral IF
- urine B12 levels measured

# UPPER GASTROINTESTINAL BLEEDING

Patients may present with the following:

- Haematemesis and/ or malaena
- Epigastric discomfort
- Sudden collapse

The extent to which these will occur will depend upon the source. Mortality is higher in patients presenting with haematemesis than malaena alone.

### Oesophageal bleeding

| Cause | Presenting features |
|---|---|
| Oesophagitis | Small volume of fresh blood, often streaking vomit. Malaena rare. Often ceases spontaneously. Usually history of antecedent GORD type symptoms. |
| Cancer | Usually small volume of blood, except as pre terminal event with erosion of major vessels. Often associated symptoms of dysphagia and constitutional symptoms such as weight loss. May be recurrent until malignancy managed. |
| Mallory Weiss Tear | Typically brisk small to moderate volume of bright red blood following bout of repeated vomiting. Malaena rare. Usually ceases spontaneously. |
| Varices | Usually large volume of fresh blood. Swallowed blood may cause malaena. Often associated with haemodynamic compromise. May stop spontaneously but re-bleeds are common until appropriately managed. |

### Gastric Bleeding

| Cause | Presenting features |
|---|---|
| Gastric cancer | May be frank haematemesis or altered blood mixed with vomit. Usually prodromal features of dyspepsia and may have constitutional symptoms. Amount of bleeding variable but erosion of major vessel may produce considerable haemorrhage. |
| Dieulafoy Lesion | Often no prodromal features prior to haematemesis and malaena, but this arteriovenous malformation may produce quite considerable haemorrhage and may be difficult to detect endoscopically |
| Diffuse erosive gastritis | Usually haematemesis and epigastric discomfort. Usually there is an underlying cause such as recent NSAID usage. Large volume haemorrhage may occur with considerable haemodynamic compromise |
| Gastric ulcer | Small low volume bleeds more common so would tend to present as iron deficiency anaemia. Erosion into a significant vessel may produce considerable haemorrhage and haematemesis. |

### Duodenum

Most common cause of major haemorrhage is a posteriorly sited duodenal ulcer. However, ulcers at any site in the duodenum may present with haematemesis, malaena and epigastric discomfort. The pain of duodenal ulcer is slightly different to that of gastric ulcers and often occurs several hours after eating. Peri ampullary tumours may bleed but these are rare. In patients with previous abdominal aortic aneurysm surgery aorto-enteric fistulation remains a rare but important cause of major haemorrhage associated with high mortality.

**Management**

- Admission to hospital careful monitoring, cross match blood, check FBC, LFTs, U+E and Clotting (as a minimum)
- Patients with on-going bleeding and haemodynamic instability are likely to require O negative blood pending cross matched blood
- Early control of airway is vital (e.g. Drowsy patient with liver failure)
- Patients with suspected varices should receive terlipressin prior to endoscopy
- Ideally all patients admitted with upper gastrointestinal haemorrhage should undergo Upper GI endoscopy within 24 hours of admission. In those who are unstable this should occur immediately after resuscitation or in tandem with it. The endoscopy department is a potentially dangerous place for unstable patients and it may be safer to perform the endoscopy in theatre with an anaesthetist present.
- Varices should be banded or subjected to sclerotherapy. If this is not possible owing to active bleeding then a Sengaksten- Blakemore tube (or Minnesota tube) should be inserted. This should be done with care; gastric balloon should be inflated first and oesophageal balloon second. Remember the balloon with need deflating after 12 hours (ideally sooner) to prevent necrosis. Portal pressure should be lowered by combination of medical therapy +/- TIPSS.
- Patients with erosive oesophagitis / gastritis should receive a proton pump inhibitor.
- Mallory Weiss tears will typically resolve spontaneously
- Identifiable bleeding points should receive combination therapy of injection of adrenaline and either a thermal or mechanical treatment. All who have received intervention should receive a continuous infusion of a proton pump inhibitor (IV omeprazole for 72 hours) to reduce the re-bleeding rate.
- Patients with diffuse erosive gastritis who cannot be managed endoscopically and continue to bleed may require gastrectomy
- Bleeding ulcers that cannot be controlled endoscopically may require laparotomy and ulcer underruning

Indications for surgery

- Patients > 60 years
- Continued bleeding despite endoscopic intervention
- Recurrent bleeding
- Known cardiovascular disease with poor response to hypotension

**Surgery**
**Duodenal ulcer**

Laparotomy, duodenotomy and under running of the ulcer. If bleeding is brisk then the ulcer is almost always posteriorly sited and will have invaded the gastroduodenal artery. Large bites using 0 Vicryl are taken above and below the ulcer base to occlude the vessel. The duodenotomy should be longitudinal but closed transversely to avoid stenosis.

**For gastric ulcer**
Under-running of the bleeding site
Partial gastrectomy-antral ulcer
Partial gastrectomy or under running the ulcer- lesser curve ulcer (involving left gastric artery)
Total gastrectomy if bleeding persists

**Summary of Acute Upper GI bleeding recommendations:**
The need for admission and timing of endoscopic intervention may be predicted by using the Blatchford score. This considers a patients Hb, serum urea, pulse rate and blood pressure. Those patients with a score of 0 are low risk, all others are considered high risk and require admission and endoscopy.
The requirement for pre endoscopic proton pump inhibition is contentious. In the UK the National Institute of Clinical Excellence guidelines suggest the pre endoscopic PPI therapy is unnecessary. Whilst it is accepted that such treatment has no impact on mortality or morbidity a Cochrane review of this practice in 2007 did suggest that it reduced the stigmata or recent haemorrhage at endoscopy. As a result many will still administer PPI to patients prior to endoscopic intervention.
Following endoscopy it is important to calculate the Rockall score for patients to determine their risk of rebleeding and mortality. A score of 3 or less is associated with a rebleeding rate of 4% and a very low risk of mortality and identifies a group of patients suitable for early discharge.

**References**

1. http://www.sign.ac.uk/guidelines/fulltext/105/index.html
2. Joint Advisory Group on Endoscopy (JAG) Guidelines - http://www.thejag.org.uk
3. NICE Guideline: Management of acute upper GI bleeding. July 2012.

# ACUTE UPPER GASTROINTESTINAL BLEEDING

NICE published guidelines in 2012 on the management of acute upper gastrointestinal bleeding which is most commonly due to either peptic ulcer disease or oesophageal varices. Some of the key points are detailed below.

**Risk assessment**

- use the Blatchford score at first assessment, and
- the full Rockall score after endoscopy

**Blatchford score**

| Admission risk marker | Score |
|---|---|
| Urea (mmol/l) | 6·5 - 8 = 2<br>8 - 10 = 3<br>10 - 25 = 4<br>> 25 = 6 |
| Haemoglobin (g/l) | Men<br>• 12 - 13 = 1<br>• 10 - 12 = 3<br>• < 10 = 6<br>Women<br>• 10 - 12 = 1<br>• < 10 = 6 |
| Systolic blood pressure (mmHg) | 100 - 109 = 1<br>90 - 99 = 2<br>< 90 = 3 |
| Other markers | Pulse >=100/min = 1<br>Presentation with melaena = 1<br>Presentation with syncope = 2<br>Hepatic disease = 2<br>Cardiac failure = 2 |

Patients with a Blatchford score of 0 may be considered for early discharge.

**Resuscitation**
- ABC, wide-bore intravenous access * 2
- platelet transfusion if actively bleeding platelet count of less than 50 x 10*9/litre
- fresh frozen plasma to patients who have either a fibrinogen level of less than 1 g/litre, or a prothrombin time (international normalised ratio) or activated partial thromboplastin time greater than 1.5 times normal
- prothrombin complex concentrate to patients who are taking warfarin and actively bleeding

**Endoscopy**
- should be offered immediately after resuscitation in patients with a severe bleed
- all patients should have endoscopy within 24 hours

**Management of non-variceal bleeding**
- NICE do not recommend the use of proton pump inhibitors (PPIs) before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding although PPIs should be given to

patients with non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy
- if further bleeding then options include repeat endoscopy, interventional radiology and surgery

**Management of variceal bleeding**
- terlipressin and prophylactic antibiotics should be given to patients at presentation (i.e. before endoscopy)
- band ligation should be used for oesophageal varices and injections of N-butyl-2-cyanoacrylate for patients with gastric varices
- transjugular intrahepatic portosystemic shunts (TIPS) should be offered if bleeding from varices is not controlled with the above measures

# VARICEAL HAEMORRHAGE

Acute treatment of variceal haemorrhage
- ABC: patients should ideally be resuscitated prior to endoscopy
- correct clotting: FFP, vitamin K
- vasoactive agents: terlipressin is currently the only licensed vasoactive agent and is supported by NICE guidelines. It has been shown to be of benefit in initial haemostasis and preventing rebleeding. Octreotide may also be used although there is some evidence that terlipressin has a greater effect on reducing mortality
- prophylactic antibiotics have been shown to reduce mortality in patients with liver cirrhosis. Quinolones are typically used. NICE support this in their 2016 guidelines: *'Offer prophylactic intravenous antibiotics for people with cirrhosis who have upper gastrointestinal bleeding.'*
- endoscopy: endoscopic variceal band ligation is superior to endoscopic sclerotherapy. NICE recommend band ligation
- Sengstaken-Blakemore tube if uncontrolled haemorrhage
- Transjugular Intrahepatic Portosystemic Shunt (TIPSS) if above measures fail

Prophylaxis of variceal haemorrhage
- propranolol: reduced rebleeding and mortality compared to placebo
- endoscopic variceal band ligation (EVL) is superior to endoscopic sclerotherapy. It should be performed at two-weekly intervals until all varices have been eradicated. Proton pump inhibitor cover is given to prevent EVL-induced ulceration. This is supported by NICE who recommend: *'Offer endoscopic variceal band ligation for the primary prevention of bleeding for people with cirrhosis who have medium to large oesophageal varices.'*

# ZOLLINGER-ELLISON SYNDROME

Zollinger-Ellison syndrome is condition characterised by excessive levels of gastrin, usually from a gastrin secreting tumour usually of the duodenum or pancreas. Around 30% occur as part of MEN type I syndrome

Features
- multiple gastroduodenal ulcers
- diarrhoea
- malabsorption

Diagnosis
- fasting gastrin levels: the single best screen test
- secretin stimulation test

## JEJUNAL VILLOUS ATROPHY

Whilst coeliac disease is the classic cause of jejunal villous atrophy there are a number of other causes you need to be aware of

Causes
- coeliac disease
- tropical sprue
- hypogammaglobulinaemia
- gastrointestinal lymphoma
- Whipple's disease
- cow's milk intolerance

## WHIPPLE'S DISEASE

Whipple's disease is a rare multi-system disorder caused by Tropheryma whippelii infection. It is more common in those who are HLA-B27 positive and in middle-aged men.

Features
- malabsorption: diarrhoea, weight loss
- large-joint arthralgia
- lymphadenopathy
- skin: hyperpigmentation and photosensitivity
- pleurisy, pericarditis
- neurological symptoms (rare): ophthalmoplegia, dementia, seizures, ataxia, myoclonus

Investigation

- jejunal biopsy shows deposition of macrophages containing Periodic acid-Schiff (PAS) granules

Management
- guidelines vary: oral co-trimoxazole for a year is thought to have the lowest relapse rate, sometimes preceded by a course of IV penicillin

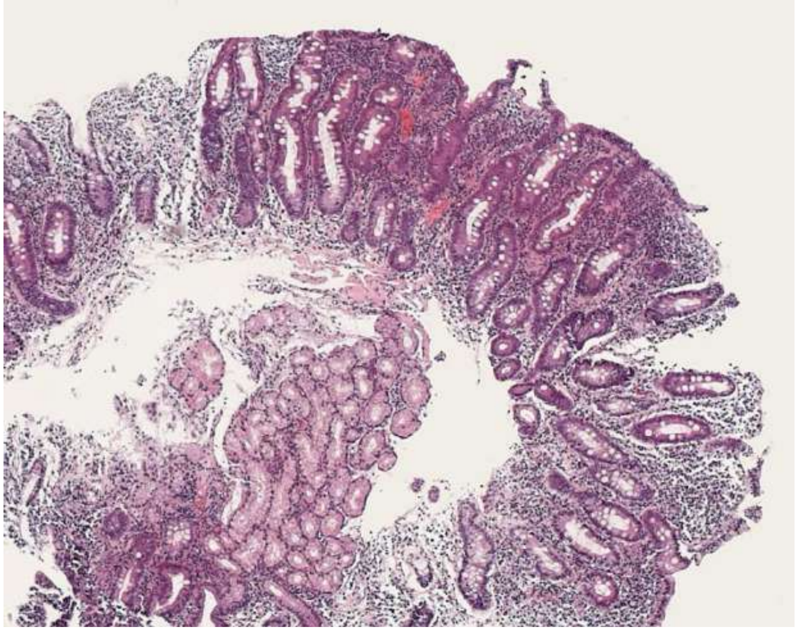
# COELIAC DISEASE

Coeliac disease is an autoimmune condition caused by sensitivity to the protein gluten. It is thought to affect around 1% of the UK population. Repeated exposure leads to villous atrophy which in turn causes malabsorption. Conditions associated with coeliac disease include dermatitis herpetiformis (a vesicular, pruritic skin eruption) and autoimmune disorders (type 1 diabetes mellitus and autoimmune hepatitis). It is strongly associated with HLA-DQ2 (95% of patients) and HLA-DQ8 (80%).

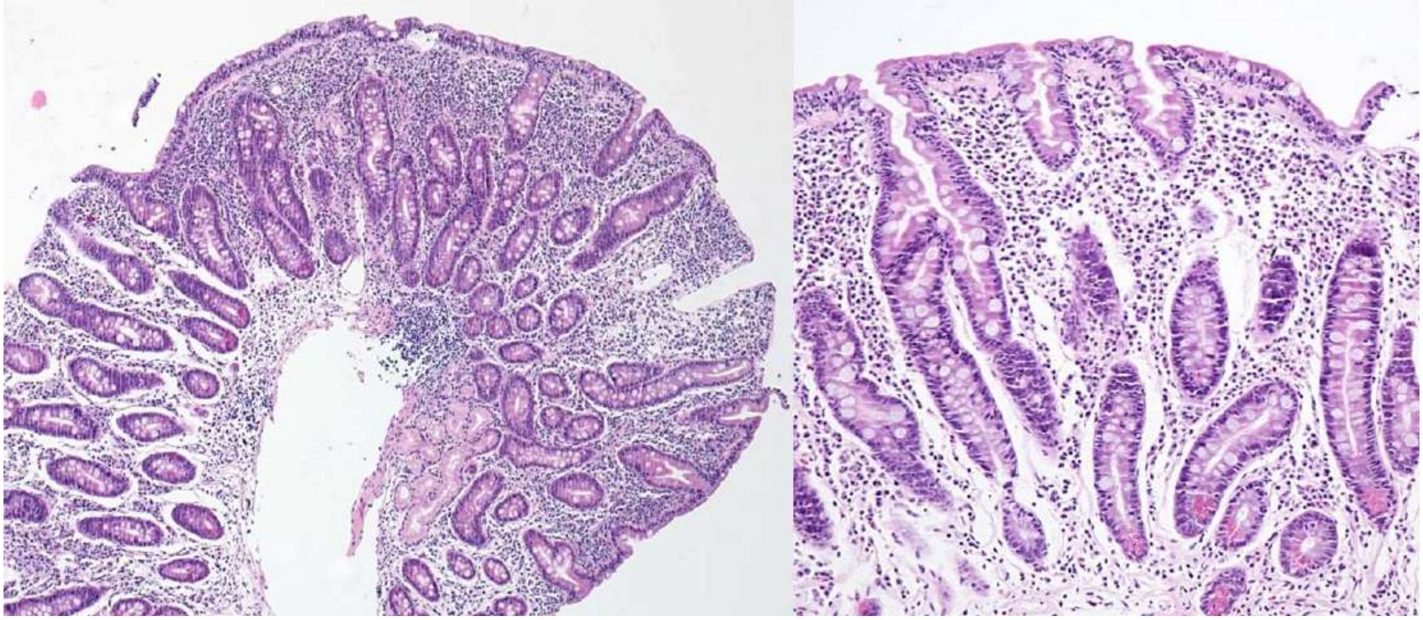
In 2009 NICE issued guidelines on the investigation of coeliac disease. They suggest that the following patients should be screened for coeliac disease:

| Signs and symptoms | Conditions |
|---|---|
| • Chronic or intermittent diarrhoea<br>• Failure to thrive or faltering growth (in children)<br>• Persistent or unexplained gastrointestinal symptoms including nausea and vomiting<br>• Prolonged fatigue ('tired all the time')<br>• Recurrent abdominal pain, cramping or distension<br>• Sudden or unexpected weight loss<br>• Unexplained iron-deficiency anaemia, or other unspecified anaemia | • Autoimmune thyroid disease<br>• Dermatitis herpetiformis<br>• Irritable bowel syndrome<br>• Type 1 diabetes<br>• First-degree relatives (parents, siblings or children) with coeliac disease |

Complications
- anaemia: iron, folate and vitamin B12 deficiency (folate deficiency is more common than vitamin B12 deficiency in coeliac disease)
- hyposplenism
- osteoporosis, osteomalacia
- lactose intolerance
- enteropathy-associated T-cell lymphoma of small intestine
- subfertility, unfavourable pregnancy outcomes
- rare: oesophageal cancer, other malignancies



Duodenal biopsy from a patient with coeliac disease. Complete atrophy of the villi with flat mucosa and marked crypt hyperplasia. Intraepithelial lymphocytosis. Dense mixed inflammatory infiltrate in the lamina propria.



Duodenal biopsy from a patient with coeliac disease. Flat mucosa with hyperplastic crypts and dense cellular infiltrate in the lamina propria. Increased number of intraepithelial lymphocytes and vacuolated superficial epithelial cell vacuolated superficial epithelial cells. Higher magnification image on the right.

*these are also occasionally performed from the jejunum

# COELIAC DISEASE: INVESTIGATION

Coeliac disease is caused by sensitivity to the protein gluten. Repeated exposure leads to villous atrophy which in turn causes malabsorption. Conditions associated with coeliac disease include dermatitis herpetiformis (a vesicular, pruritic skin eruption) and autoimmune disorders (type 1 diabetes mellitus and autoimmune hepatitis).

Diagnosis is made by a combination of immunology and jejunal biopsy. Villous atrophy and immunology normally reverses on a gluten-free diet.

NICE issued guidelines on the investigation of coeliac disease in 2009. If patients are already taking a gluten-free diet they should be asked, if possible, to reintroduce gluten for at least 6 weeks prior to testing.

Immunology
- tissue transglutaminase (TTG) antibodies (IgA) are first-choice according to NICE
- endomyseal antibody (IgA)
    - needed to look for selective IgA deficiency, which would give a false negative coeliac result
- anti-gliadin antibody (IgA or IgG) tests are not recommended by NICE
- anti-casein antibodies are also found in some patients

Duodenal biopsy*
- villous atrophy
- crypt hyperplasia
- increase in intraepithelial lymphocytes
- lamina propria infiltration with lymphocytes

Rectal gluten challenge has been described but is not widely used

## COELIAC DISEASE: MANAGEMENT

The management of coeliac disease involves a gluten-free diet. Gluten-containing cereals include:
- wheat: bread, pasta, pastry
- barley: beer
    - whisky is made using malted barley. Proteins such as gluten are however removed during the distillation process making it safe to drink for patients with coeliac disease
- rye
- oats
    - some patients with coeliac disease appear able to tolerate oats

Some notable foods which are gluten-free include:
- rice
- potatoes

- corn (maize)

Tissue transglutaminase antibodies may be checked to check compliance with a gluten-free diet.

Immunisation
- Patients with coeliac disease often have a degree of **functional hyposplenism**
- For this reason, all patients with coeliac disease are offered the pneumococcal vaccine
    - Coeliac UK recommends that everyone with coeliac disease is vaccinated against pneumococcal infection and has a booster every 5 years
- Currrent guidelines suggest giving the influenza vaccine on an individual basis.

# SMALL BOWEL BACTERIAL OVERGROWTH SYNDROME

Small bowel bacterial overgrowth syndrome (SBBOS) is a disorder characterised by excessive amounts of bacteria in the small bowel resulting in gastrointestinal symptoms.

Risk factors for SBBOS
- neonates with congenital gastrointestinal abnormalities
- scleroderma
- diabetes mellitus

It should be noted that many of the features overlap with irritable bowel syndrome:
- chronic diarrhoea
- bloating, flatulence
- abdominal pain

Diagnosis
- hydrogen breath test
- small bowel aspiration and culture: this is used less often as invasive and results are often difficult to reproduce
- clinicians may sometimes give a course of antibiotics as a diagnostic trial

Management
- correction of underlying disorder
- antibiotic therapy: rifaximin is now the treatment of choice due to relatively low resistance. Co-amoxiclav or metronidazole are also effective in the majority of patients.

# MALABSORPTION

Malabsorption is characterised by diarrhoea, steatorrhoea and weight loss. Causes may be broadly divided into intestinal (e.g. villous atrophy), pancreatic (deficiency of pancreatic enzyme production or secretion) and biliary (deficiency of bile-salts needed for emulsification of fats)

Intestinal causes of malabsorption
- coeliac disease
- Crohn's disease
- tropical sprue
- Whipple's disease
- Giardiasis
- brush border enzyme deficiencies (e.g. lactase insufficiency)

Pancreatic causes of malabsorption
- chronic pancreatitis
- cystic fibrosis
- pancreatic cancer

Biliary causes of malabsorption
- biliary obstruction
- primary biliary cirrhosis

Other causes
- bacterial overgrowth (e.g. systemic sclerosis, diverticulae, blind loop)
- short bowel syndrome
- lymphoma

# MALNUTRITION

Malnutrition is an important consequence of and contributor to chronic disease. It is clearly a complex and multifactorial problem that can be difficult to manage but there are a number of key points to remember for the exam.

NICE define malnutrition as the following:
- a Body Mass Index (BMI) of less than 18.5; or
- unintentional weight loss greater than 10% within the last 3-6 months; or
- a BMI of less than 20 and unintentional weight loss greater than 5% within the last 3-6 months

Around 10% of patients aged over 65 years are malnourished, the vast majority of those living independently, i.e. not in hospital or care/nursing homes.

Screening for malnutrition if mostly done using MUST (Malnutrition Universal Screen Tool). A link is provided to a copy of the MUST score algorithm.

- it should be done on admission to care/nursing homes and hospital, or if there is concern. For example an elderly, thin patient with pressure sores
- it takes into account BMI, recent weight change and the presence of acute disease
- categorises patients into low, medium and high risk

Management of malnutrition is difficult. NICE recommend the following points:
- dietician support if the patient is high-risk
- a 'food-first' approach with clear instructions (e.g. 'add full-fat cream to mashed potato'), rather than just prescribing oral nutritional supplements (ONS) such as Ensure
- if ONS are used they should be taken between meals, rather than instead of meals

# REFEEDING SYNDROME

Refeeding syndrome describes the metabolic abnormalities which occur on feeding a person following a period of starvation. It occurs when an extended period of catabolism ends abruptly with switching to carbohydrate metabolism. The metabolic consequences include:
- hypophosphataemia
- hypokalaemia
- hypomagnesaemia: may predispose to torsades de pointes
- abnormal fluid balance

These abnormalities can lead to organ failure.

**Prevention**
NICE produced guidelines in 2006 on nutritional support. Refeeding syndrome may avoided by identifying patients at a high-risk of developing refeeding syndrome:

Patients are considered high-risk if one or more of the following:
- BMI < 16 kg/m2
- unintentional weight loss >15% over 3-6 months
- little nutritional intake > 10 days
- hypokalaemia, hypophosphataemia or hypomagnesaemia prior to feeding (unless high)

If two or more of the following:
- BMI < 18.5 kg/m2
- unintentional weight loss > 10% over 3-6 months
- little nutritional intake > 5 days
- history of: alcohol abuse, drug therapy including insulin, chemotherapy, diuretics and antacids

NICE recommend that if a patient hasn't eaten for > 5 days, aim to re-feed at no more than 50% of requirements for the first 2 days.

# OBESITY: BARIATRIC SURGERY

The use of bariatric surgery in the management of obesity has developed significantly over the past decade. It is now recognised that for many obese patients who fail to lose weight with lifestyle and drug interventions the risks and expense of long-term obesity outweigh those of surgery.

**NICE guidelines on bariatric surgery for adults**
Consider surgery for people with severe obesity if:

- they have a BMI of 40 kg/m^2 or more, or between 35 kg/m^2 and 40 kg/m^2 and other significant disease (for example, type 2 diabetes mellitus, hypertension) that could be improved if they lost weight
- all appropriate non-surgical measures have failed to achieve or maintain adequate clinically beneficial weight loss for at least 6 months
- they are receiving or will receive intensive specialist management
- they are generally fit for anaesthesia and surgery
- they commit to the need for long-term follow-up

Consider surgery as a first-line option for adults with a BMI of more than 50 kg/m2 in whom surgical intervention is considered appropriate; consider orlistat before surgery if the waiting time is long

Types of bariatric surgery:

- primarily restrictive: laparoscopic-adjustable gastric banding (LAGB) or sleeve gastrectomy
- primarily malabsorptive: classic biliopancreatic diversion (BPD) has now largely been replaced by biliopancreatic diversion with duodenal switch
- mixed: Roux-en-Y gastric bypass surgery

Which operation?

- LAGB produces less weight loss than malabsorptive or mixed procedures but as it has fewer complications it is normally the first-line intervention in patients with a BMI of 30-39kg/m^2
- patients with a BMI > 40 kg/m^2 may be considered for a gastric bypass or sleeve gastrectomy. The latter may be done as a sole procedure or as an initial procedure prior to bypass
- primarily malabsorptive procedures are usually reserved for very obese patients (e.g. BMI > 60 kg/m^2)

# ABDOMINAL PAIN

The table below gives characteristic exam question features for conditions causing abdominal pain. Unusual and 'medical' causes of abdominal pain should also be remembered:

- myocardial infarction
- diabetic ketoacidosis

- pneumonia
- acute intermittent porphyria
- lead poisoning

| Condition | Characteristic exam feature |
|---|---|
| Peptic ulcer disease | Duodenal ulcers: more common than gastric ulcers, epigastric pain relieved by eating<br>Gastric ulcers: epigastric pain worsened by eating<br>Features of upper gastrointestinal haemorrhage may be seen (haematemesis, melena etc) |
| Appendicitis | Pain initial in the central abdomen before localising to the right iliac fossa<br>Anorexia is common<br>Tachycardia, low-grade pyrexia, tenderness in RIF<br>Rovsing's sign: more pain in RIF than LIF when palpating LIF |
| Acute pancreatitis | Usually due to alcohol or gallstones<br>Severe epigastric pain<br>Vomiting is common<br>Examination may reveal tenderness, ileus and low-grade fever<br>Periumbilical discolouration (Cullen's sign) and flank discolouration (Grey-Turner's sign) is described but rare |
| Biliary colic | Pain in the RUQ radiating to the back and interscapular region, may be following a fatty meal. Slight misnomer as the pain may persist for hours<br>Obstructive jaundice may cause pale stools and dark urine<br>It is sometimes taught that patients are female, forties, fat and fair although this is obviously a generalisation |
| Acute cholecystitis | History of gallstones symptoms (see above)<br>Continuous RUQ pain<br>Fever, raised inflammatory markers and white cells<br>Murphy's sign positive (arrest of inspiration on palpation of the RUQ) |
| Diverticulitis | Colicky pain typically in the LLQ<br>Fever, raised inflammatory markers and white cells |
| Abdominal aortic aneurysm | Severe central abdominal pain radiating to the back<br>Presentation may be catastrophic (e.g. Sudden collapse) or sub-acute (persistent severe central abdominal pain with developing shock)<br>Patients may have a history of cardiovascular disease |
| Intestinal obstruction | History of malignancy/previous operations<br>Vomiting<br>Not opened bowels recently<br>'Tinkling' bowel sounds |

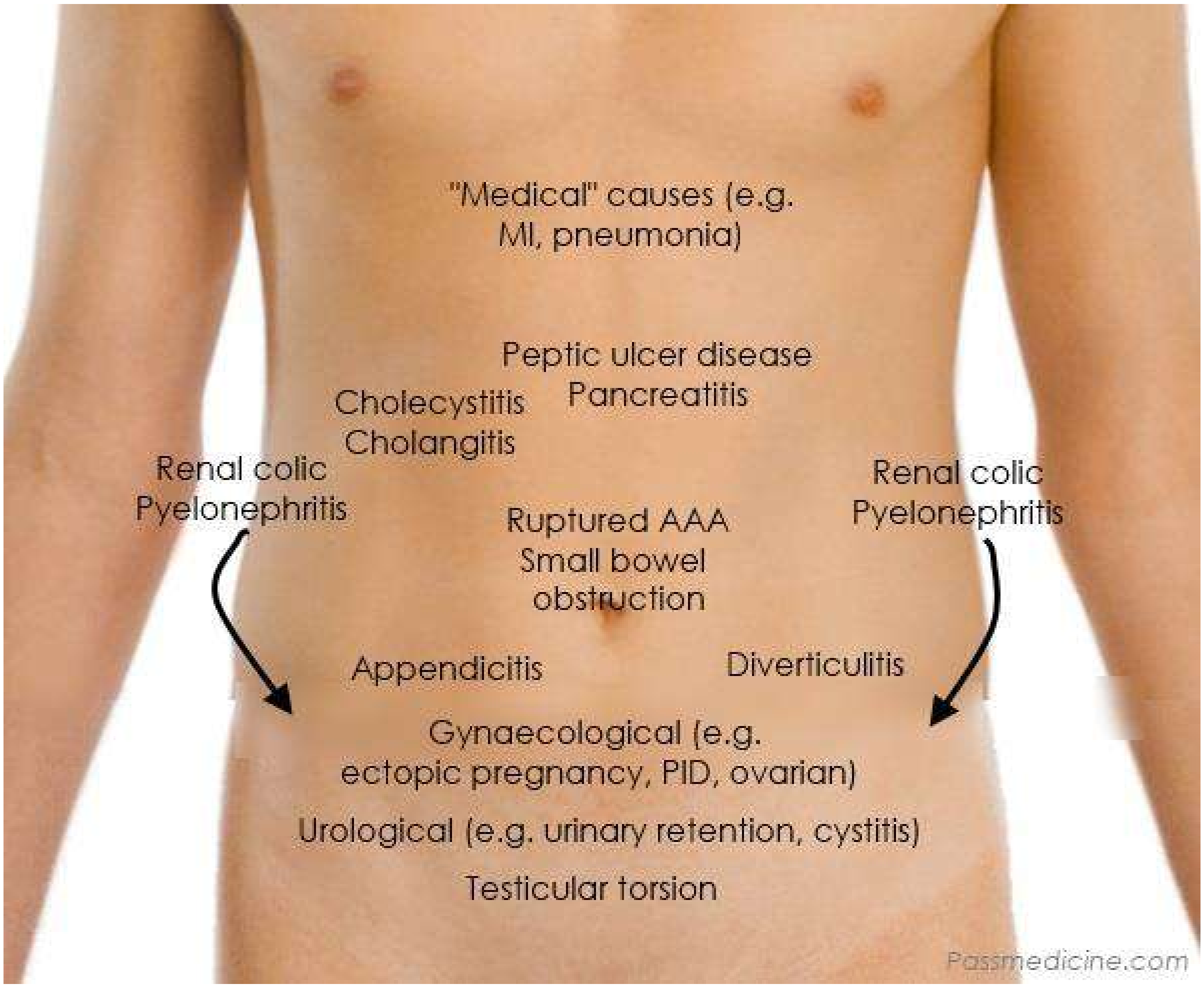

"Medical" causes (e.g. MI, pneumonia)
Peptic ulcer disease
Pancreatitis
Cholecystitis
Cholangitis
Renal colic
Pyelonephritis
Renal colic
Pyelonephritis
Ruptured AAA
Small bowel obstruction
Appendicitis
Diverticulitis
Gynaecological (e.g. ectopic pregnancy, PID, ovarian)
Urological (e.g. urinary retention, cystitis)
Testicular torsion
Passmedicine.com

Diagram showing stereotypical areas where particular conditions present. The diagram is not exhaustive and only lists the more common conditions seen in clinical practice. Note how pain from renal causes such as renal/ureteric colic and pyelonephritis may radiate and move from the loins towards the suprapubic area.

## GALLSTONES

Up to 24% of women and 12% of men may have gallstones. Of these up to 30% may develop local infection and cholecystitis. In patients subjected to surgery, 12% will have stones contained within the common bile duct. The majority of gallstones are of a mixed composition (50%) with pure cholesterol stones accounting for 20% of cases.

The aetiology of CBD stones differs in the world, in the West most CBD stones are the result of migration. In the East, a far higher proportion arise in the CBD de novo.

The classical symptoms are of colicky right upper quadrant pain that occurs postprandially. The symptoms are usually worst following a fatty meal when cholecystokinin levels are highest and gallbladder contraction is maximal.

**Investigation**

In almost all suspected cases the standard diagnostic workup consists of abdominal ultrasound and liver function tests. Of patients who have stones within the bile duct, 60% will have at least one abnormal result on LFT's. Ultrasound is an important test, but is operator dependent and therefore may occasionally need to be repeated if a negative result is at odds with the clinical picture. Where stones are suspected in the bile duct the options lie between magnetic resonance cholangiography and intraoperative imaging. The choice between these two options is determined by the skills and experience of the surgeon. The advantages of intraoperative imaging are less useful in making therapeutic decisions if the operator is unhappy about proceeding the bile duct exploration, and in such circumstances, preoperative MRCP is probably a better option.

### Specific gallstone and gallbladder related disease

| Disease | Features | Management |
|---|---|---|
| Biliary colic | Colicky abdominal pain, worse postprandially, worse after fatty foods | If imaging shows gallstones and history compatible then laparoscopic cholecystectomy |
| Acute cholecystitis | Right upper quadrant pain<br>Fever<br>Murphys sign on examination<br>Occasionally mildly deranged LFT's (especially if Mirizzi syndrome) | Imaging (USS) and cholecystectomy (ideally within 48 hours of presentation) (2) |
| Gallbladder abscess | Usually prodromal illness and right upper quadrant pain<br>Swinging pyrexia<br>Patient may be systemically unwell<br>Generalised peritonism not present | Imaging with USS +/- CT Scanning<br>Ideally, surgery although subtotal cholecystectomy may be needed if Calot's triangle is hostile<br>In unfit patients, percutaneous drainage may be considered |
| Cholangitis | Patient severely septic and unwell<br>Jaundice<br>Right upper quadrant pain | Fluid resuscitation<br>Broad-spectrum intravenous antibiotics<br>Correct any coagulopathy<br>Early ERCP |
| Gallstone ileus | Patients may have a history of previous cholecystitis and known gallstones<br>Small bowel obstruction (may be intermittent) | Laparotomy and removal of the gallstone from small bowel, the enterotomy must be made proximal to the site of obstruction and not at the site of obstruction. The fistula between the gallbladder and duodenum should not be interfered with. |
| Acalculous cholecystitis | Patients with intercurrent illness (e.g. diabetes, organ failure)<br>Patient of systemically | If patient fit then cholecystectomy, if unfit then percutaneous cholecystostomy |

| Disease | Features | Management |
|---|---|---|
|  | unwell<br>Gallbladder inflammation in absence of stones<br>High fever |  |

**Treatment**

Asymptomatic gallstones which are located in the gallbladder are common and do not require treatment. However, if stones are present in the common bile duct there is an increased risk of complications such as cholangitis or pancreatitis and surgical management should be considered.

Patients with asymptomatic gallstones rarely develop symptoms related to them (less than 2% per year) and may, therefore, be managed expectantly. In almost all cases of symptomatic gallstones the treatment of choice is cholecystectomy performed via the laparoscopic route. In the very frail patient, there is sometimes a role for the selective use of ultrasound guided cholecystostomy.

During the course of the procedure, some surgeons will routinely perform either intraoperative cholangiography to either confirm anatomy or to exclude CBD stones. The latter may be more easily achieved by use of laparoscopic ultrasound. If stones are found then the options lie between early ERCP in the day or so following surgery or immediate surgical exploration of the bile duct. When performed via the trans cystic route this adds little in the way of morbidity and certainly results in faster recovery. Where transcystic exploration fails the alternative strategy is that of formal choledochotomy. The exploration of a small duct is challenging and ducts of less than 8mm should not be explored. Small stones that measure less than 5mm may be safely left and most will pass spontaneously.

Risks of ERCP(1)
- Bleeding 0.9% (rises to 1.5% if sphincterotomy performed)
- Duodenal perforation 0.4%
- Cholangitis 1.1%
- Pancreatitis 1.5%

**References**

1. Williams E et al. Guidelines on the management of common bile duct stones (CBDS)Gut 2008;57:10041021

2. Gurusamy KS, Samraj K. Early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD005440.

# POST-CHOLECYSTECTOMY SYNDROME

Post-cholecystectomy syndrome is a recognised complication of cholecystectomies. Typically symptoms of dyspepsia, vomiting, pain, flatulence and diarrhoea occur in up to 40% patients post surgery.

The pathology behind the syndrome isn't completely clear, however there is some association with remnant stones and biliary injury. Pain is often due to sphincter of Oddi dysfunction and the development of surgical adhesions.

Management is often difficult, but often involves a low-fat diet and the introduction of bile acid sequestrants, such as Cholestyramine, to bind the excess bile acids and thus preventing lower gastrointestinal signs. Proton-pump inhibitors like Lansoprazole do play a role, if the patient is complaining of dyspeptic like symptoms. Antibiotics and pancreatic enzyme replacements play no part in management.

# ACUTE APPENDICITIS

Acute appendicitis is the most common acute abdominal condition requiring surgery. It can occur at any age but is most common in young people aged 10-20 years.

Abdominal pain is seen in the vast majority of patients:

- peri-umbilical abdominal pain (visceral stretching of appendix lumen and appendix is midgut structure) radiating to the right iliac fossa (RIF) due to localised parietal peritoneal inflammation.
- the migration of the pain from the centre to the RIF has been shown to be one of the strongest indicators of appendicitis
- patients often report the pain being worse on coughing or going over speed bumps. Children typically can't hop on the right leg due to the pain.

Other features:

- vomit once or twice but marked and persistent vomiting is unusual
- diarrhoea is rare. However, pelvic appendicitis may cause localised rectal irritation of some loose stools. A pelvic abscess may also cause diarrhoea
- mild pyrexia is common - temperature is usually 37.5-38oC. Higher temperatures are more typical of conditions like mesenteric adenitis
- anorexia is very common. It is very unusual for patients with appendicitis to be hungry
- around 50% of patients have the typical symptoms of anorexia, peri-umbilical pain and nausea followed by more localised right lower quadrant pain

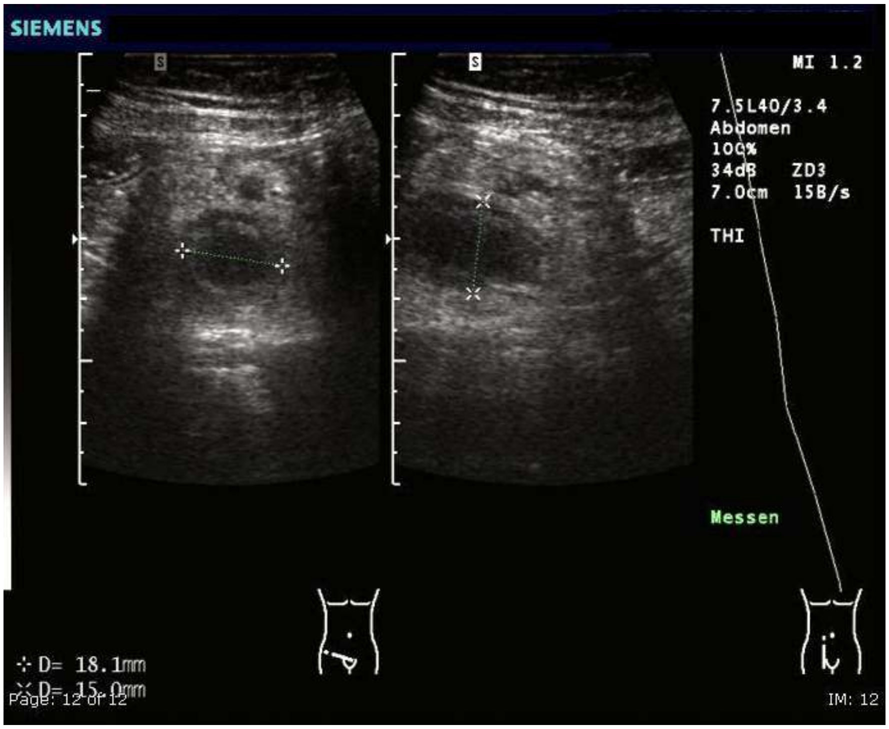
Examination

- generalised peritonitis if perforation has occurred or localised peritonism
- retrocaecal appendicitis may have relatively few signs

- digital rectal examination may reveal boggy sensation if pelvic abscess is present, or even right-sided tenderness with a pelvic appendix
- Rovsing's sign (palpation in the LIF causes pain in the RIF) is now thought to be of limited value

Diagnosis
- typically raised inflammatory markers coupled with compatible history and examination findings should be enough to justify appendicectomy
- a neutrophil-predominant leucocytosis is seen in 80-90%
- urine analysis: useful to exclude pregnancy in women, renal colic and urinary tract infection. In patients with appendicitis, urinalysis may show mild leucocytosis but no nitrites
- ultrasound is useful in females where pelvic organ pathology is suspected. Although it is not always possible to visualise the appendix on ultrasound, the presence of free fluid (always pathological in males) should raise suspicion
- CT scans are widely used in patients with suspected appendicitis in the US but this practice has not currently reached the UK, due to the concerns regarding excessive ionising radiation and resource limitations

Management
- appendicectomy which can be performed via either an open or laparoscopic approach. Laparoscopic appendicectomy is now the treatment of choice
- administration of prophylactic intravenous antibiotics reduces wound infection rates
- patients with perforated appendicitis (typical around 15-20%) require copious abdominal lavage.
- patients without peritonitis who have an appendix mass should receive broad-spectrum antibiotics and consideration given to performing an interval appendicectomy.
- be wary in the older patients who may have either an underlying caecal malignancy or perforated sigmoid diverticular disease.
- trials have looked at the use of intravenous antibiotics alone in the treatment of appendicitis. The evidence currently suggests that whilst this is successful in the majority of patients, it is associated with a longer hospital stay and up to 20% of patients go on to have an appendicectomy within 12 months.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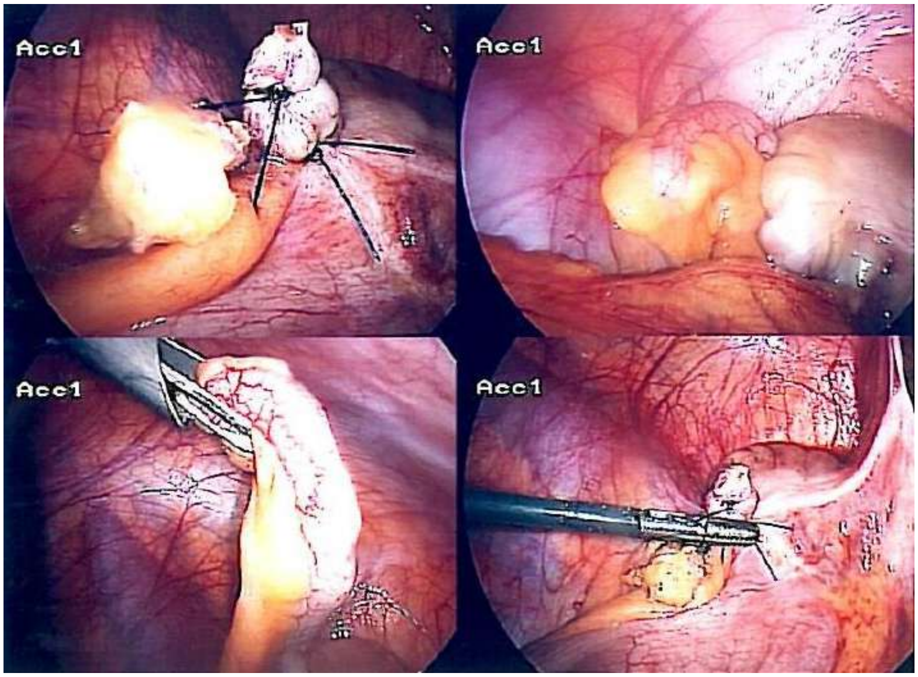
Ultrasound examination may show evidence of lumenal obstruction and thickening of the appendiceal wall as shown below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Laparoscopic appendicectomy is becoming increasing popular as demonstrated below

# DIVERTICULOSIS

Diverticulosis is an extremely common disorder characterised by multiple outpouchings of the bowel wall, most commonly in the sigmoid colon. Strictly speaking the term diverticular disease is reserved for patients who are symptomatic - diverticulosis is the more accurate term for diverticula being present.

Risk factors
- increasing age
- low-fibre diet

Diverticulosis can present in a number of ways:
- painful diverticular disease: altered bowel habit, colicky left sided abdominal pain. A high fibre diet is usually recommended to minimise symptoms
- diverticulitis: see below for more details

**Diverticulitis**
One of the diverticular become infected. The classical presentation is:
- left iliac fossa pain and tenderness
- anorexia, nausea and vomiting
- diarrhoea
- features of infection (pyrexia, raised WBC and CRP)

Management:
- mild attacks can be treated with oral antibiotics
- more significant episodes are managed in hospital. Patients are made nil by mouth, intravenous fluids and intravenous antibiotics (typical a cephalosporin + metronidazole) are given

Complications of diverticulitis include:
- abscess formation
- peritonitis
- obstruction
- perforation

# INHERITED CAUSES OF JAUNDICE

There are 4 inherited causes of jaundice you need to be aware of: Gilbert's syndrome, Crigler-Najjar syndrome, Dubin-Johnson syndrome and Rotor's syndrome. It is important for the exam to be able to classify them according to whether they cause conjugated or unconjugated hyperbilirubinaemia:

| Unconjugated hyperbilirubinaemia | Conjugated hyperbilirubinaemia |
|---|---|
| Gilbert's syndrome<br>Crigler-Najjar syndrome | Dubin-Johnson syndrome<br>Rotor syndrome |

**Important points for the exam:**

Gilbert's syndrome
- autosomal recessive
- mild deficiency of UDP-glucuronyl transferase
- benign

Crigler-Najjar syndrome, type 1
- autosomal recessive
- absolute deficiency of UDP-glucuronosyl transferase
- do not survive to adulthood

Crigler-Najjar syndrome, type 2
- slightly more common than type 1 and less severe
- may improve with phenobarbital

Dubin-Johnson syndrome
- autosomal recessive. Relatively common in Iranian Jews
- mutation in the canalicular multidrug resistance protein 2 (MRP2) results in defective hepatic excretion of bilirubin
- results in a grossly black liver
- benign

Rotor syndrome
- autosomal recessive
- defect in the hepatic uptake and storage of bilirubin
- benign

# PREGNANCY: JAUNDICE

### Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (also known as obstetric cholestasis) occurs in around 1% of pregnancies and is generally seen in the third trimester. It is the most common liver disease of pregnancy.

Features
- pruritus, often in the palms and soles
- no rash (although skin changes may be seen due to scratching)

- raised bilirubin

Management
- ursodeoxycholic acid is used for symptomatic relief
- weekly liver function tests
- women are typically induced at 37 weeks

Complications include an increased rate of stillbirth. It is not generally associated with increased maternal morbidity

**Acute fatty liver of pregnancy**
Acute fatty liver of pregnancy is rare complication which may occur in the third trimester or the period immediately following delivery.

Features
- abdominal pain
- nausea & vomiting
- headache
- jaundice
- hypoglycaemia
- severe disease may result in pre-eclampsia

Investigations
- ALT is typically elevated e.g. 500 u/l

Management
- support care
- once stabilised delivery is the definitive management

Gilbert's, Dubin-Johnson syndrome, may be exacerbated during pregnancy

HELLP
- Haemolysis, Elevated Liver enzymes, Low Platelets

# CHOLESTYRAMINE

Cholestyramine is a bile acid sequestrant used in the management of hyperlipidaemia. It decreases bile acid reabsorption in the small intestine, therefore upregulating the amount of cholesterol that is converted to bile acid. The main effect it has on the lipid profile is to reduce LDL cholesterol. It is also occasionally used in Crohn's disease for treatment-resistant diarrhoea.

Adverse effects

- abdominal cramps and constipation
- decreases absorption of fat-soluble vitamins
- cholesterol gallstones
- may raise level of triglycerides

# BILE-ACID MALABSORPTION

Bile-acid malabsorption is a cause of chronic diarrhoea. This may be primary, due to excessive production of bile acid, or secondary to an underlying gastrointestinal disorder causing reduced bile acid absorption. It can lead to steatorrhoea and vitamin A, D, E, K malabsorption.

- Secondary causes are often seen in patients with ileal disease, such as with Crohn's. Other secondary causes include:
- cholecystectomy
- coeliac disease
- small intestinal bacterial overgrowth

Investigation
- the test of choice is **SeHCAT**
- nuclear medicine test using a gamma-emitting selenium molecule in selenium homocholic acid taurine or tauroselcholic acid (SeHCAT)
- scans are done 7 days apart to assess the retention/loss of radiolabelled 75SeHCAT

Management
- bile acid sequestrants e.g. cholestyramine

# BUDD-CHIARI SYNDROME

Budd-Chiari syndrome, or hepatic vein thrombosis, is usually seen in the context of underlying haematological disease or another procoagulant condition.

Causes
- polycythaemia rubra vera
- thrombophilia: activated protein C resistance, antithrombin III deficiency, protein C & S deficiencies
- pregnancy
- oral contraceptive pill

The features are classically a triad of:
- abdominal pain: sudden onset, severe

- ascites
- tender hepatomegaly

Investigations
- ultrasound with Doppler flow studies is very sensitive and should be the initial radiological investigation

# DRUG-INDUCED LIVER DISEASE

Drug-induced liver disease is generally divided into hepatocellular, cholestatic or mixed. There is however considerable overlap, with some drugs causing a range of changes to the liver

The following drugs tend to cause a hepatocellular picture:
- paracetamol
- sodium valproate, phenytoin
- MAOIs
- halothane
- anti-tuberculosis: isoniazid, rifampicin, pyrazinamide
- statins
- alcohol
- amiodarone
- methyldopa
- nitrofurantoin

The following drugs tend to cause cholestasis (+/- hepatitis):
- combined oral contraceptive pill
- antibiotics: flucloxacillin, co-amoxiclav, erythromycin*
- anabolic steroids, testosterones
- phenothiazines: chlorpromazine, prochlorperazine
- sulphonylureas
- fibrates
- rare reported causes: nifedipine

Liver cirrhosis
- methotrexate
- methyldopa
- amiodarone

*risk may be reduced with erythromycin stearate

# ACUTE LIVER FAILURE

Acute liver failure describes the rapid onset of hepatocellular dysfunction leading to a variety of systemic complications.

Causes
- paracetamol overdose
- alcohol
- viral hepatitis (usually A or B)
- acute fatty liver of pregnancy

Features*
- jaundice
- coagulopathy: raised prothrombin time
- hypoalbuminaemia
- hepatic encephalopathy
- renal failure is common ('hepatorenal syndrome')

*remember that 'liver function tests' do not always accurately reflect the synthetic function of the liver. This is best assessed by looking at the prothrombin time and albumin level.

# COAGULOPATHY OF LIVER DISEASE

In liver failure all clotting factors are low, except for factor VIII which is paradoxically supra-normal. This is because factor VIII is synthesised in endothelial cells throughout the body, unlike the other clotting factors which are synthesised purely in hepatic endothelial cells. Furthermore, whilst activated factor VIII is usually rapidly cleared from the blood stream, good hepatic function is required for this to occur, further leading to increases in circulating factor VIII. This is one of many reasons why, despite conventional coagulation studies (increased PT, APTT, decreased fibrinogen) suggesting increased bleeding risk, patients with chronic liver disease are not protected from venous thrombosis formation but are paradoxically at an increased risk of thrombosis, in addition to bleeding. Other events occurring in chronic liver disease which predispose patients to thrombosis formation include reduced synthesis of the purely hepatic derived natural anticoagulants protein c and protein s (vitamin k dependent), and anti-thrombin (non-vitamin k dependent).

Reference

Tripodi et al. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterology. 2009 Dec;137(6):2105-11.

# HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy may be seen in liver disease of any cause. The aetiology is not fully understood but is thought to include excess absorption of ammonia and glutamine from bacterial breakdown of proteins in the gut.

Whilst hepatic encephalopathy is often associated with acute liver failure it may also be seen with chronic disease. It is now recognised that many patients with liver cirrhosis may develop subtle symptoms such as mild cognitive impairment before the features become more recognisable ('minimal' or 'covert' hepatic encephalopathy). It has also been noted that portal venous bypass with portosystemic shunting (for example post transjugular intrahepatic portosystemic shunt).

Features
- confusion, altered GCS (see below)
- asterix: 'liver flap', arrhythmic negative myoclonus with a frequency of 3-5 Hz
- constructional apraxia: inability to draw a 5-pointed star
- triphasic slow waves on EEG
- raised ammonia level (not commonly measured anymore)

Grading of hepatic encephalopathy
- Grade I: Irritability
- Grade II: Confusion, inappropriate behaviour
- Grade III: Incoherent, restless
- Grade IV: Coma

Precipitating factors
- infection e.g. spontaneous bacterial peritonitis
- GI bleed
- post transjugular intrahepatic portosystemic shunt
- constipation
- drugs: sedatives, diuretics
- hypokalaemia
- renal failure
- increased dietary protein (uncommon)

Management
- treat any underlying precipitating cause
- NICE recommend lactulose first-line, with the addition of rifaximin for the secondary prophylaxis of hepatic encephalopathy
- lactulose is thought to work by promoting the excretion of ammonia and increasing the metabolism of ammonia by gut bacteria
- antibiotics such as rifaximin are thought to modulate the gut flora resulting in decreased ammonia production

- other options include embolisation of portosystemic shunts and liver transplantation in selected patients

# ACUTE PANCREATITIS

Acute pancreatitis is usually due to alcohol or gallstones.

Pathophysiology:
- autodigestion of pancreatic tissue by the pancreatic enzymes, leading to necrosis

Features:
- Severe epigastric pain that may radiate through to the back
- Vomiting is common
- Examination may reveal tenderness, ileus and low-grade fever
- Periumbilical discolouration (Cullen's sign) and flank discolouration (Grey-Turner's sign) is described but rare

Rare features associated with pancreatitis include:
- ischaemic (Purtscher) retinopathy - may cause temporary or permanent blindness

Investigations:
- raised amylase is seen in 75% of patients.

**Scoring systems**

There are several scoring systems used to identify cases of severe pancreatitis which may require intensive care management. These include the Ranson score, Glasgow score and APACHE II.

Some common factors indicating severe pancreatitis include:
- age > 55 years
- hypocalcaemia
- hyperglycaemia
- hypoxia
- neutrophilia
- elevated LDH and AST

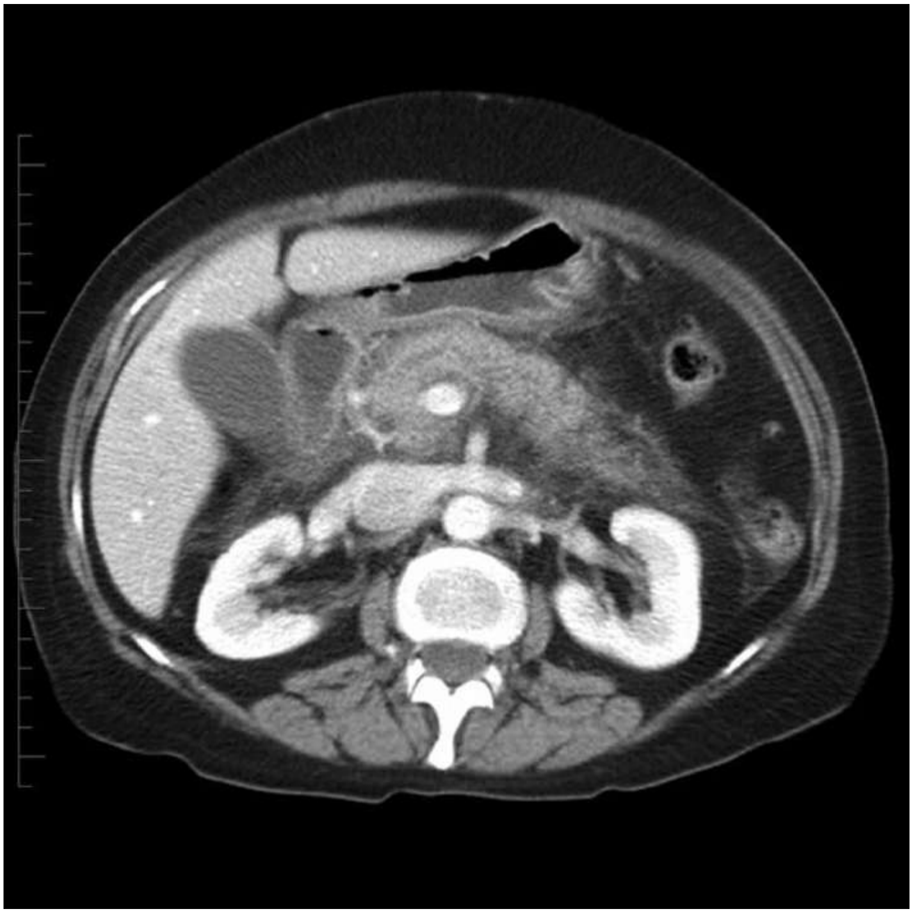
Note that the actual amylase level is not of prognostic value.

# ACUTE PANCREATITIS: CAUSES

The vast majority of cases in the UK are caused by gallstones and alcohol.

Popular mnemonic is **GET SMASHED**

- **G**allstones
- **E**thanol
- **T**rauma
- **S**teroids
- **M**umps (other viruses include Coxsackie B)
- **A**utoimmune (e.g. polyarteritis nodosa), Ascaris infection
- **S**corpion venom
- **H**ypertriglyceridaemia, **H**yperchylomicronaemia, **H**ypercalcaemia, **H**ypothermia
- **E**RCP
- **D**rugs (azathioprine, mesalazine*, didanosine, bendroflumethiazide, furosemide, pentamidine, steroids, sodium valproate)



CT from a patient with acute pancreatitis. Note the diffuse parenchymal enlargement with oedema and indistinct margins.

*pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine

# ACUTE PANCREATITIS: COMPLICATIONS

**Local complications**

Peripancreatic fluid collections

- Occur in 25% cases
- Located in or near the pancreas and lack a wall of granulation or fibrous tissue
- May resolve or develop into pseudocysts or abscesses
- Since most resolve aspiration and drainage is best avoided as it may precipitate infection

Pseudocysts

- In acute pancreatitis result from organisation of peripancreatic fluid collection. They may or may not communicate with the ductal system.
- The collection is walled by fibrous or granulation tissue and typically occurs 4 weeks or more after an attack of acute pancreatitis
- Most are retrogastric
- 75% are associated with persistent mild elevation of amylase
- Investigation is with CT, ERCP and MRI or endoscopic USS
- Symptomatic cases may be observed for 12 weeks as up to 50% resolve
- Treatment is either with endoscopic or surgical cystogastrostomy or aspiration

Pancreatic necrosis

- Pancreatic necrosis may involve both the pancreatic parenchyma and surrounding fat
- Complications are directly linked to extent of parenchymal necrosis and extent of necrosis overall
- Early necrosectomy is associated with a high mortality rate (and should be avoided unless compelling indications for surgery exist)
- Sterile necrosis should be managed conservatively (at least initially)
- Some centres will perform fine-needle aspiration sampling of necrotic tissue if infection is suspected. False negatives may occur and the extent of sepsis and organ dysfunction may be a better guide to surgery

Pancreatic abscess

- Intraabdominal collection of pus associated with pancreas but in the absence of necrosis
- Typically occur as a result of infected pseudocyst
- Transgastric drainage is one method of treatment, endoscopic drainage is an alternative

Haemorrhage

- Infected necrosis may involve vascular structures with resultant haemorrhage that may occur de novo or as a result of surgical necrosectomy.
- When retroperitoneal haemorrhage occurs Grey Turner's sign may be identified

**Systemic complications**

Acute respiratory distress syndrome

- associated with a high-mortality rate of around 20%

# ACUTE PANCREATITIS: MANAGEMENT

**Management of Acute Pancreatitis in the UK**

**Diagnosis**

- Traditionally hyperamylasaemia has been utlilised with amylase being elevated three times the normal range.
- However, amylase may give both false positive and negative results.
- Serum lipase is both more sensitive and specific than serum amylase. It also has a longer half life.
- Serum amylase levels do not correlate with disease severity.

*Differential causes of hyperamylasaemia*

| |
|---|
| Acute pancreatitis |
| Pancreatic pseudocyst |
| Mesenteric infarct |
| Perforated viscus |
| Acute cholecystitis |
| Diabetic ketoacidosis |

**Assessment of severity**

- Glasgow, Ranson scoring systems and APACHE II
- Biochemical scoring e.g. using CRP

*Features that may predict a severe attack within 48 hours of admission to hospital*

| | |
|---|---|
| **Initial assessment** | • Clinical impression of severity<br>• Body mass index >30<br>• Pleural effusion<br>• APACHE score >8 |
| **24 hours after admission** | • Clinical impression of severity<br>• APACHE II >8<br>• Glasgow score of 3 or more<br>• Persisting multiple organ failure<br>• CRP>150 |
| **48 hours after admission** | • Glasgow Score of >3<br>• CRP >150<br>• Persisting or progressive organ failure |

*Table adapted from UK guidelines for management of acute pancreatitis. GUT 2005, 54 suppl III*

**Management**

**Nutrition**

- There is reasonable evidence to suggest that the use of enteral nutrition does not worsen the outcome in pancreatitis
- Most trials to date were underpowered to demonstrate a conclusive benefit.
- The rationale behind feeding is that it helps to prevent bacterial translocation from the gut, thereby contributing to the development of infected pancreatic necrosis.

**Use of antibiotic therapy**

- Many UK surgeons administer antibiotics to patients with acute pancreatitis.
- A recent Cochrane review highlights the potential benefits of administering Imipenem to patients with established pancreatic necrosis in the hope of averting the progression to infection.
- There are concerns that the administration of antibiotics in mild attacks of pancreatitis will not affect outcome and may contribute to antibiotic resistance and increase the risks of antibiotic associated diarrhoea.

**Surgery**

- Patients with acute pancreatitis due to gallstones should undergo early cholecystectomy.
- Patients with obstructed biliary system due to stones should undergo early ERCP.
- Patients who fail to settle with necrosis and have worsening organ dysfunction may require debridement, fine needle aspiration is still used by some.
- Patients with infected necrosis should undergo either radiological drainage or surgical necrosectomy. The choice of procedure depends upon local expertise.

**References**

www.bsg.org.uk/pdfworddocs/pancreatic.pdf

**Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis**
Villatoro et al Cochrane Library DOI: 10.1002/14651858.CD002941.pub3. 2010 version.

# CHRONIC PANCREATITIS

Chronic pancreatitis is an inflammatory condition which can ultimately affect both the exocrine and endocrine functions of the pancreas. Around 80% of cases are due to alcohol excess with up to 20% of cases being unexplained.

Other than alcohol, causes include:

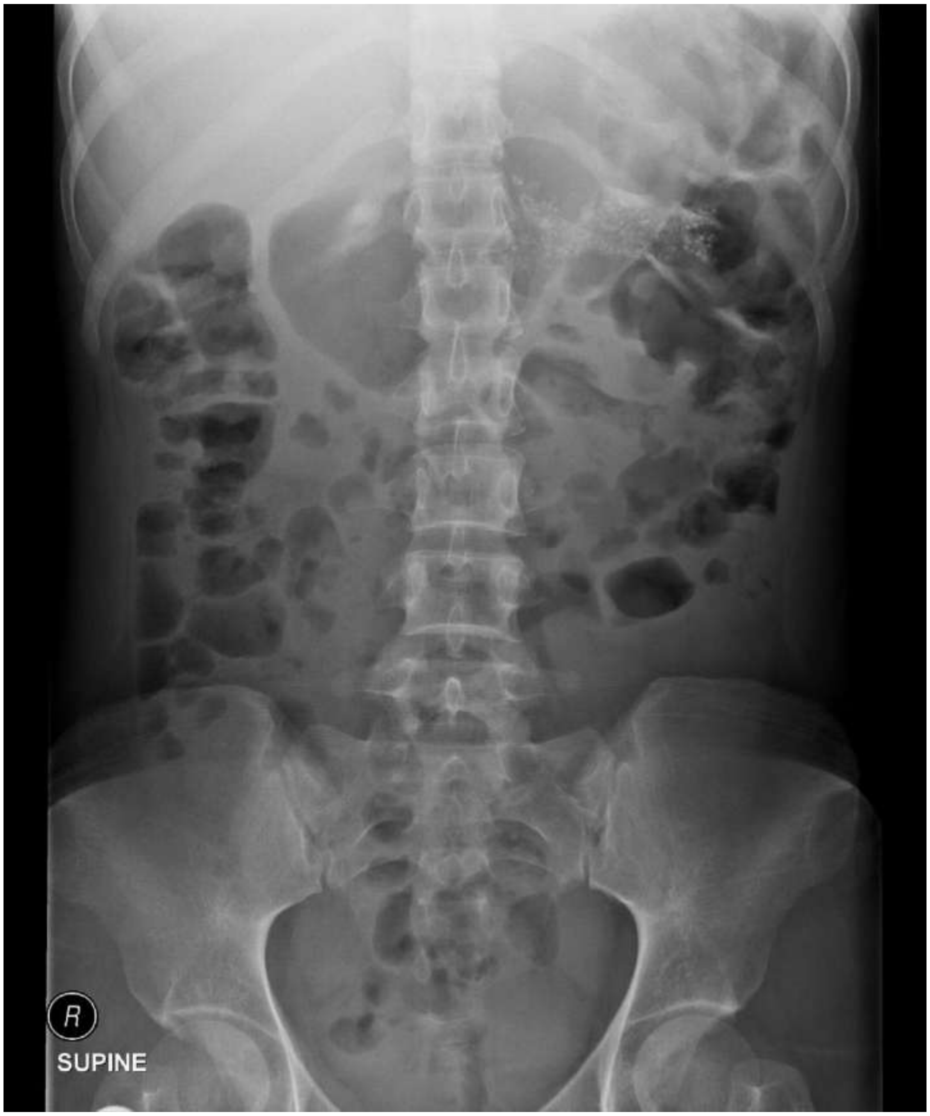
- genetic: cystic fibrosis, haemochromatosis

- ductal obstruction: tumours, stones, structural abnormalities including pancreas divisum and annular pancreas

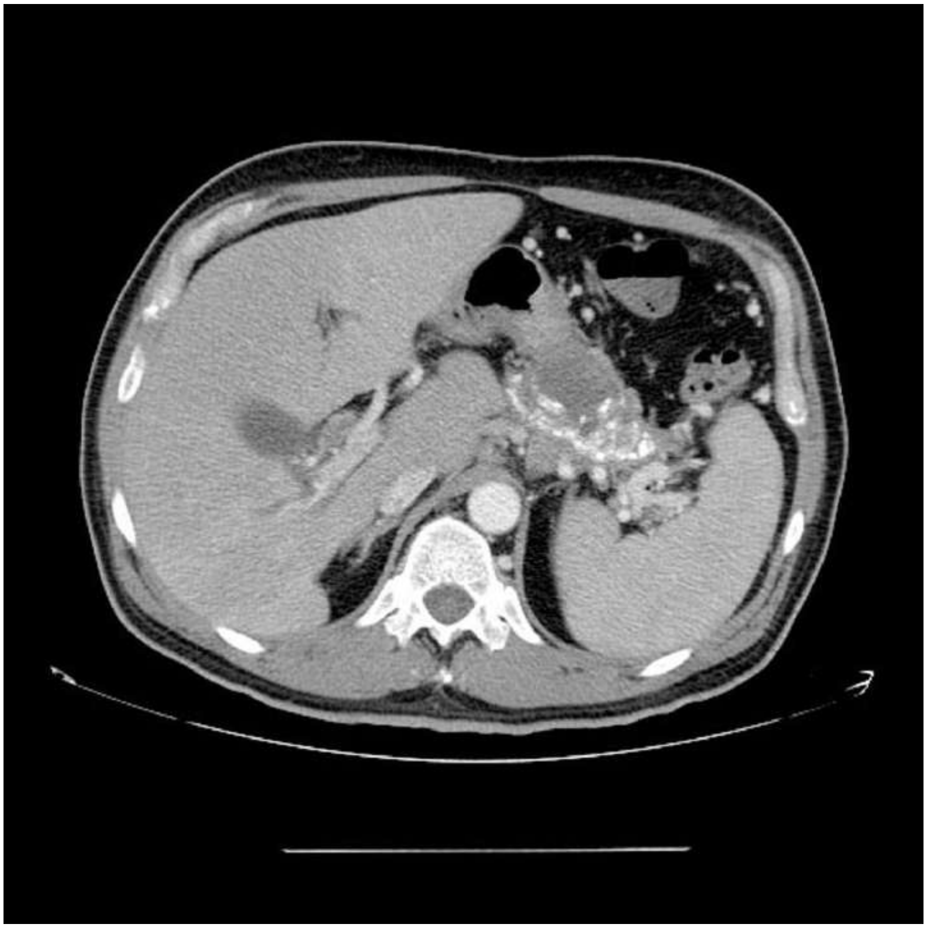
Features
- pain is typically worse 15 to 30 minutes following a meal
- steatorrhoea: symptoms of pancreatic insufficiency usually develop between 5 and 25 years after the onset of pain
- diabetes mellitus develops in the majority of patients. It typically occurs more than 20 years after symptom begin

Investigation
- abdominal x-ray shows pancreatic calcification in 30% of cases
- CT is more sensitive at detecting pancreatic calcification. Sensitivity is 80%, specificity is 85%
- functional tests: faecal elastase may be used to assess exocrine function if imaging inconclusive

Management
- pancreatic enzyme supplements
- analgesia
- antioxidants: limited evidence base - one study suggests benefit in early disease



Multiple small calcific foci projected in the pancreas consistent with chronic pancreatitis



CT showing an irregular shaped pancreas with the typical calcification of chronic pancreatitis

# PANCREATIC CANCER

Pancreatic cancer is often diagnosed late as it tends to present in a non-specific way. Over 80% of pancreatic tumours are adenocarcinomas which typically occur at the head of the pancreas.

Associations

- increasing age
- smoking
- diabetes
- chronic pancreatitis (alcohol does not appear an independent risk factor though)
- hereditary non-polyposis colorectal carcinoma
- multiple endocrine neoplasia
- BRCA2 gene
- KRAS gene mutation

Features

- classically painless jaundice

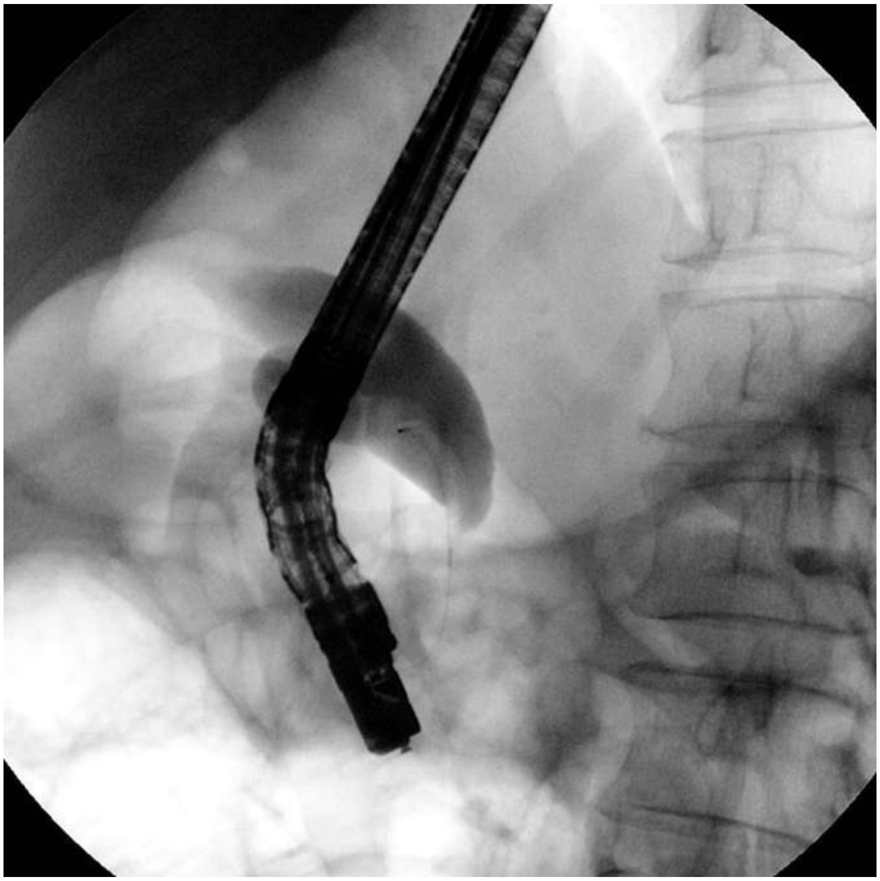
- Courvoisier's law states that in the presence of painless obstructive jaundice, a palpable gallbladder is unlikely to be due to gallstones (
- however, patients typically present in a non-specific way with anorexia, weight loss, epigastric pain
- loss of exocrine function (e.g. steatorrhoea)
- loss of endocrine function (e.g. diabetes mellitus)
- atypical back pain is often seen
- migratory thrombophlebitis (Trousseau sign) is more common than with other cancers

Investigation

- ultrasound has a sensitivity of around 60-90%
- high-resolution CT scanning is the investigation of choice if the diagnosis is suspected
- imaging may demonstrate the 'double duct' sign - the presence of simultaneous dilatation of the common bile and pancreatic ducts

Management

- less than 20% are suitable for surgery at diagnosis
- a Whipple's resection (pancreaticoduodenectomy) is performed for resectable lesions in the head of pancreas. Side-effects of a Whipple's include dumping syndrome and peptic ulcer disease
- adjuvant chemotherapy is usually given following surgery
- ERCP with stenting is often used for palliation



ERCP showing invasive ductal adenocarcinoma. Note the dilation of the common bile duct due to the pancreatic lesion

# VIPOMA

VIP (vasoactive intestinal peptide)

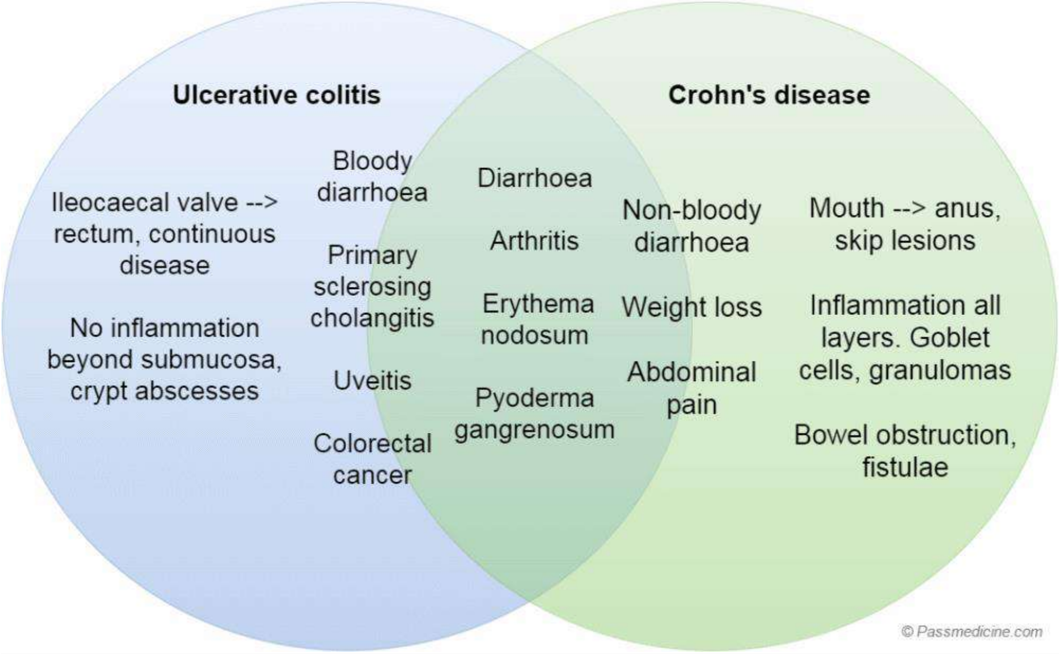
- source: small intestine, pancreas
- stimulation: neural
- actions: stimulates secretion by pancreas and intestines, inhibits acid and pepsinogen secretion

VIPoma

- 90% arise from pancreas
- large volume diarrhoea
- weight loss
- dehydration
- hypokalaemia, hypochlorhydia

# INFLAMMATORY BOWEL DISEASE: KEY DIFFERENCES

The two main types of inflammatory bowel disease are Crohn's disease and ulcerative colitis. They have many similarities in terms of presenting symptoms, investigation findings and management options.


Ulcerative colitis
Crohn's disease
Ileocaecal valve --> rectum, continuous disease
No inflammation beyond submucosa, crypt abscesses
Bloody diarrhoea
Primary sclerosing cholangitis
Uveitis
Colorectal cancer
Diarrhoea
Arthritis
Erythema nodosum
Pyoderma gangrenosum
Non-bloody diarrhoea
Weight loss
Abdominal pain
Mouth --> anus, skip lesions
Inflammation all layers. Goblet cells, granulomas
Bowel obstruction, fistulae
© Passmedicine.com

Venn diagram showing shared features and differences between ulcerative colitis and Crohn's disease. Note that whilst some features are present in both, some are much more common in one of the conditions, for example colorectal cancer in ulcerative colitis

There are however some key differences which are highlighted in table below:

| | Crohn's disease (CD) | Ulcerative colitis (UC) |
|---|---|---|
| **Features** | Diarrhoea usually non-bloody<br>Weight loss more prominent<br>Upper gastrointestinal symptoms, mouth ulcers, perianal disease<br>Abdominal mass palpable in the right iliac fossa | Bloody diarrhoea more common<br>Abdominal pain in the left lower quadrant<br>Tenesmus |
| **Extra-intestinal** | Gallstones are more common secondary to reduced bile acid reabsorption<br>Oxalate renal stones* | Primary sclerosing cholangitis more common |
| **Complications** | Obstruction, fistula, colorectal cancer | Risk of colorectal cancer high in UC than CD |
| **Pathology** | Lesions may be seen anywhere from the mouth to anus<br>Skip lesions may be present | Inflammation always starts at rectum and never spreads beyond ileocaecal valve<br>Continuous disease |
| **Histology** | Inflammation in all layers from mucosa to serosa<br>• increased goblet cells<br>• granulomas | No inflammation beyond submucosa (unless fulminant disease) - inflammatory cell infiltrate in lamina propria<br>• neutrophils migrate through the walls of glands to form crypt abscesses<br>• depletion of goblet cells and mucin from gland epithelium<br>• granulomas are infrequent |
| **Endoscopy** | Deep ulcers, skip lesions - 'cobble-stone' appearance | Widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps') |
| **Radiology** | Small bowel enema<br>• high sensitivity and specificity for examination of the terminal ileum<br>• strictures: 'Kantor's string sign'<br>• proximal bowel dilation<br>• 'rose thorn' ulcers<br>• fistulae | Barium enema<br>• loss of haustrations<br>• superficial ulceration, 'pseudopolyps'<br>• long standing disease: colon is narrow and short -'drainpipe colon' |

*impaired bile acid rebsorption increases the loss calcium in the bile. Calcium normally binds oxalate.

# CROHN'S DISEASE

Crohn's disease is a form of inflammatory bowel disease. It commonly affects the terminal ileum and colon but may be seen anywhere from the mouth to anus.

Pathology

- cause is unknown but there is a strong genetic susceptibility
- inflammation occurs in all layers, down to the serosa. This is why patients with Crohn's are prone to strictures, fistulas and adhesions

Crohn's disease typically presents in late adolescence or early adulthood. Features include:

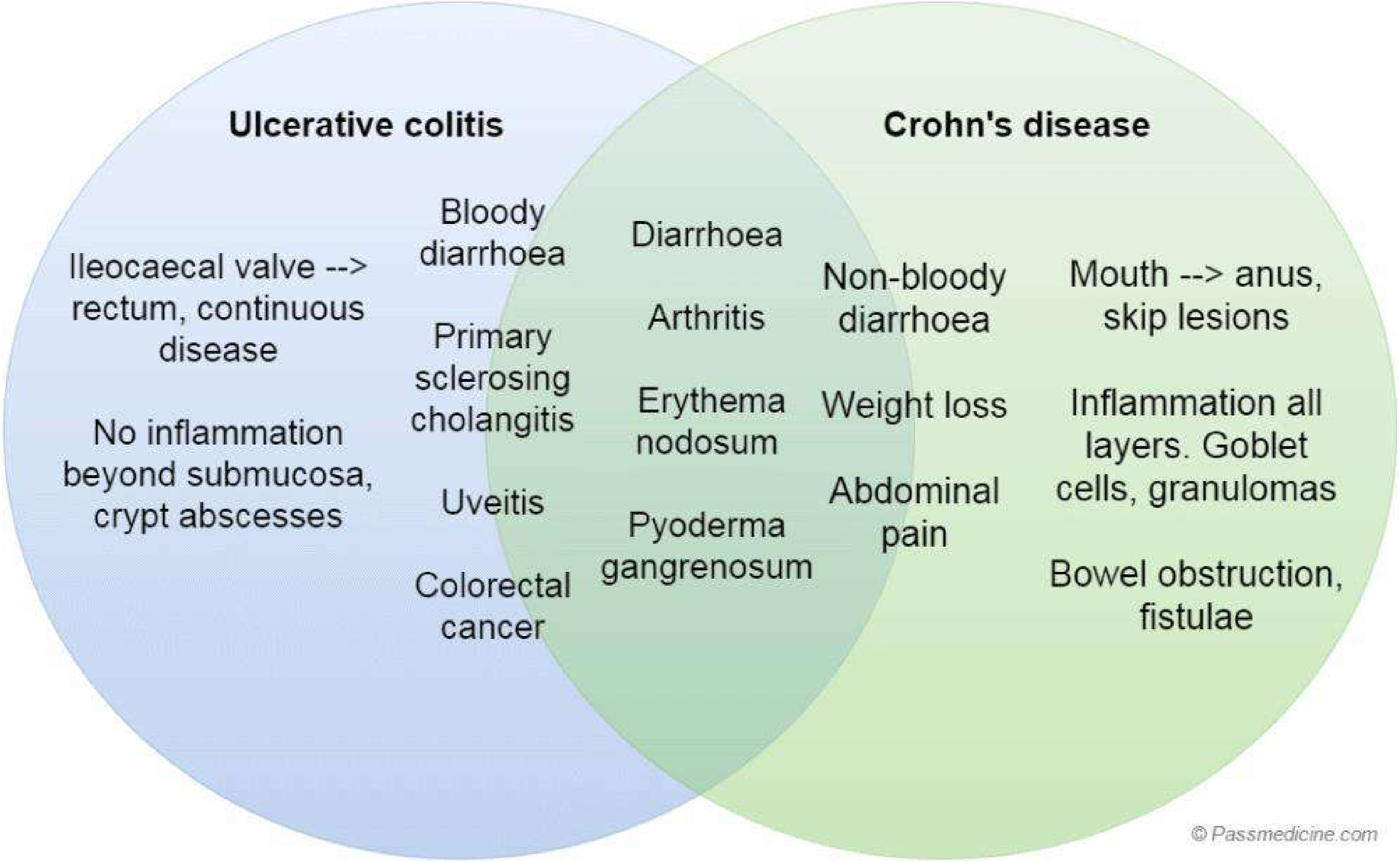
- presentation may be non-specific symptoms such as weight loss and lethargy
- diarrhoea: the most prominent symptom in adults. Crohn's colitis may cause bloody diarrhoea
- abdominal pain: the most prominent symptom in children
- perianal disease: e.g. Skin tags or ulcers
- extra-intestinal features are more common in patients with colitis or perianal disease

Investigations

- raised inflammatory markers
- increased faecal calprotectin
- anaemia
- low vitamin B12 and vitamin D

Questions regarding the 'extra-intestinal' features of inflammatory bowel disease are common:

| | **Common to both Crohn's disease (CD) and Ulcerative colitis (UC)** | **Notes** |
|---|---|---|
| **Related to disease activity** | Arthritis: pauciarticular, asymmetric<br>Erythema nodosum<br>Episcleritis<br>Osteoporosis | Arthritis is the most common extra-intestinal feature in both CD and UC<br>Episcleritis is more common in CD |
| **Unrelated to disease activity** | Arthritis: polyarticular, symmetric<br>Uveitis<br>Pyoderma gangrenosum<br>Clubbing<br>Primary sclerosing cholangitis | Primary sclerosing cholangitis is much more common in UC<br>Uveitis is more common in UC |


Ulcerative colitis
Crohn's disease
Ileocaecal valve --> rectum, continuous disease
No inflammation beyond submucosa, crypt abscesses
Bloody diarrhoea
Primary sclerosing cholangitis
Uveitis
Colorectal cancer
Diarrhoea
Arthritis
Erythema nodosum
Pyoderma gangrenosum
Non-bloody diarrhoea
Weight loss
Abdominal pain
Mouth --> anus, skip lesions
Inflammation all layers. Goblet cells, granulomas
Bowel obstruction, fistulae
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Venn diagram showing shared features and differences between ulcerative colitis and Crohn's disease. Note that whilst some features are present in both, some are much more common in one of the conditions, for example colorectal cancer in ulcerative colitis

# CROHN'S DISEASE: INVESTIGATION

Crohn's disease is a form of inflammatory bowel disease. It commonly affects the terminal ileum and colon but may be seen anywhere from the mouth to anus

Bloods

- C-reactive protein correlates well with disease activity

Endoscopy

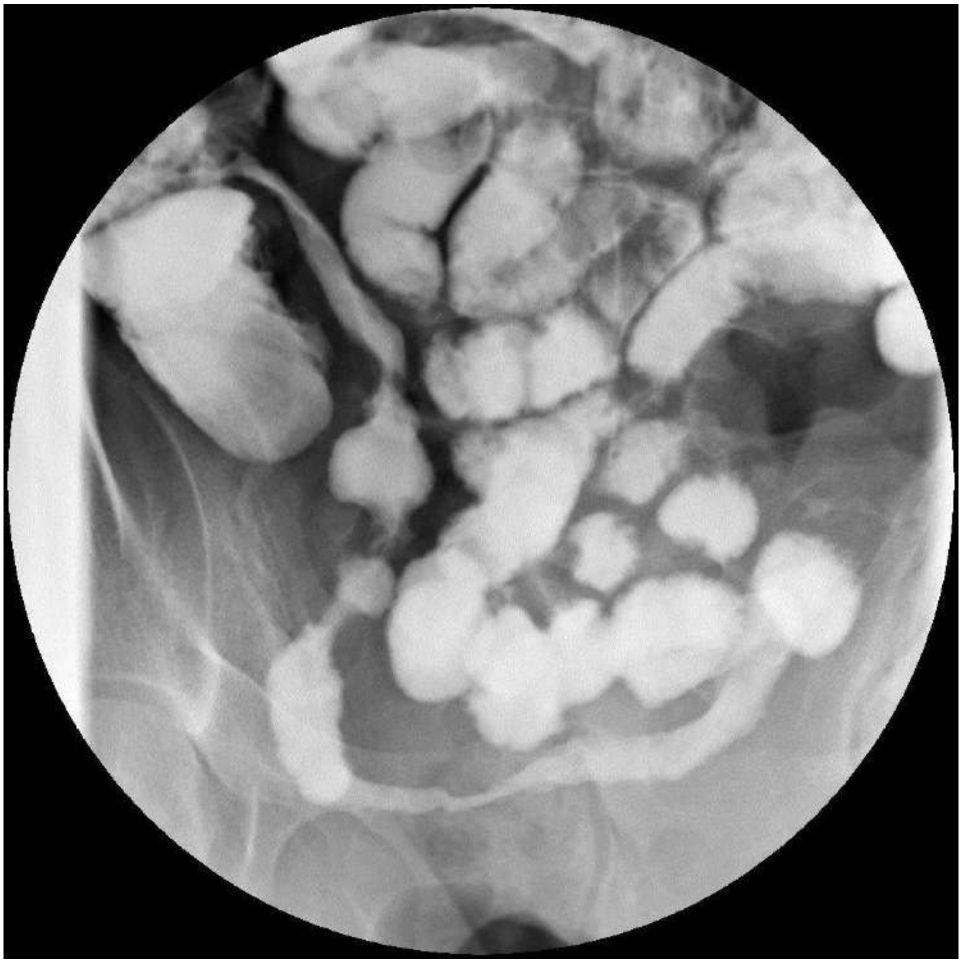
- colonoscopy is the investigation of choice
- features suggest of Crohn's include deep ulcers, skip lesions

Histology

- inflammation in all layers from mucosa to serosa
- goblet cells
- granulomas

Small bowel enema

- high sensitivity and specificity for examination of the terminal ileum
- strictures: 'Kantor's string sign'
- proximal bowel dilation
- 'rose thorn' ulcers
- fistulae



Barium study is shown from a patient with worsening Crohn's disease. Long segment of narrowed terminal ileum in a 'string like' configuration in keeping with a long stricture segment. Termed 'Kantor's string sign'.

# CROHN'S DISEASE: MANAGEMENT

Crohn's disease is a form of inflammatory bowel disease. It commonly affects the terminal ileum and colon but may be seen anywhere from the mouth to anus. NICE published guidelines on the management of Crohn's disease in 2012.

General points

- patients should be strongly advised to stop smoking
- some studies suggest an increased risk of relapse secondary to NSAIDs and the combined oral contraceptive pill but the evidence is patchy

Inducing remission

- glucocorticoids (oral, topical or intravenous) are generally used to induce remission. Budesonide is an alternative in a subgroup of patients
- enteral feeding with an elemental diet may be used in addition to or instead of other measures to induce remission, particularly if there is concern regarding the side-effects of steroids (for example in young children)
- 5-ASA drugs (e.g. mesalazine) are used second-line to glucocorticoids but are not as effective
- azathioprine or mercaptopurine* may be used as an add-on medication to induce remission but is not used as monotherapy. Methotrexate is an alternative to azathioprine
- infliximab is useful in refractory disease and fistulating Crohn's. Patients typically continue on azathioprine or methotrexate
- metronidazole is often used for isolated peri-anal disease

Maintaining remission

- as above, stopping smoking is a priority (remember: smoking makes Crohn's worse, but may help ulcerative colitis)
- azathioprine or mercaptopurine is used first-line to maintain remission
- methotrexate is used second-line
- 5-ASA drugs (e.g. mesalazine) should be considered if a patient has had previous surgery

Surgery

- around 80% of patients with Crohn's disease will eventually have surgery
- see below for further detail

**Surgical interventions in Crohn's disease**

The commonest disease pattern in Crohn's is stricturing terminal ileal disease and this often culminates in an ileocaecal resection. Other procedures performed include segmental small bowel resections and stricturoplasty. Colonic involvement in patients with Crohn's is not common and, where found, distribution is often segmental. However, despite this distribution segmental resections of the colon in patients with Crohn's disease are generally not advocated because the recurrence rate in the remaining colon is extremely high, as a result, the standard options of colonic surgery in Crohn's patients are generally; sub total colectomy, panproctocolectomy and staged sub total colectomy and proctectomy. Restorative procedures such as ileoanal pouch have no role in therapy.

Crohn's disease is notorious for the developmental of intestinal fistulae; these may form between the rectum and skin (perianal) or the small bowel and skin. Fistulation between loops of bowel may also occur and result in bacterial overgrowth and malabsorption. Management of enterocutaneous fistulae involves controlling sepsis, optimising nutrition, imaging the disease and planning definitive surgical management.

**Complications of Crohn's disease**

As well as the well-documented complications described above, patients are also at risk of:

- small bowel cancer (standard incidence ratio = 40)
- colorectal cancer (standard incidence ration = 2, i.e. less than the risk associated with ulcerative colitis)
- osteoporosis

*assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine

# ULCERATIVE COLITIS

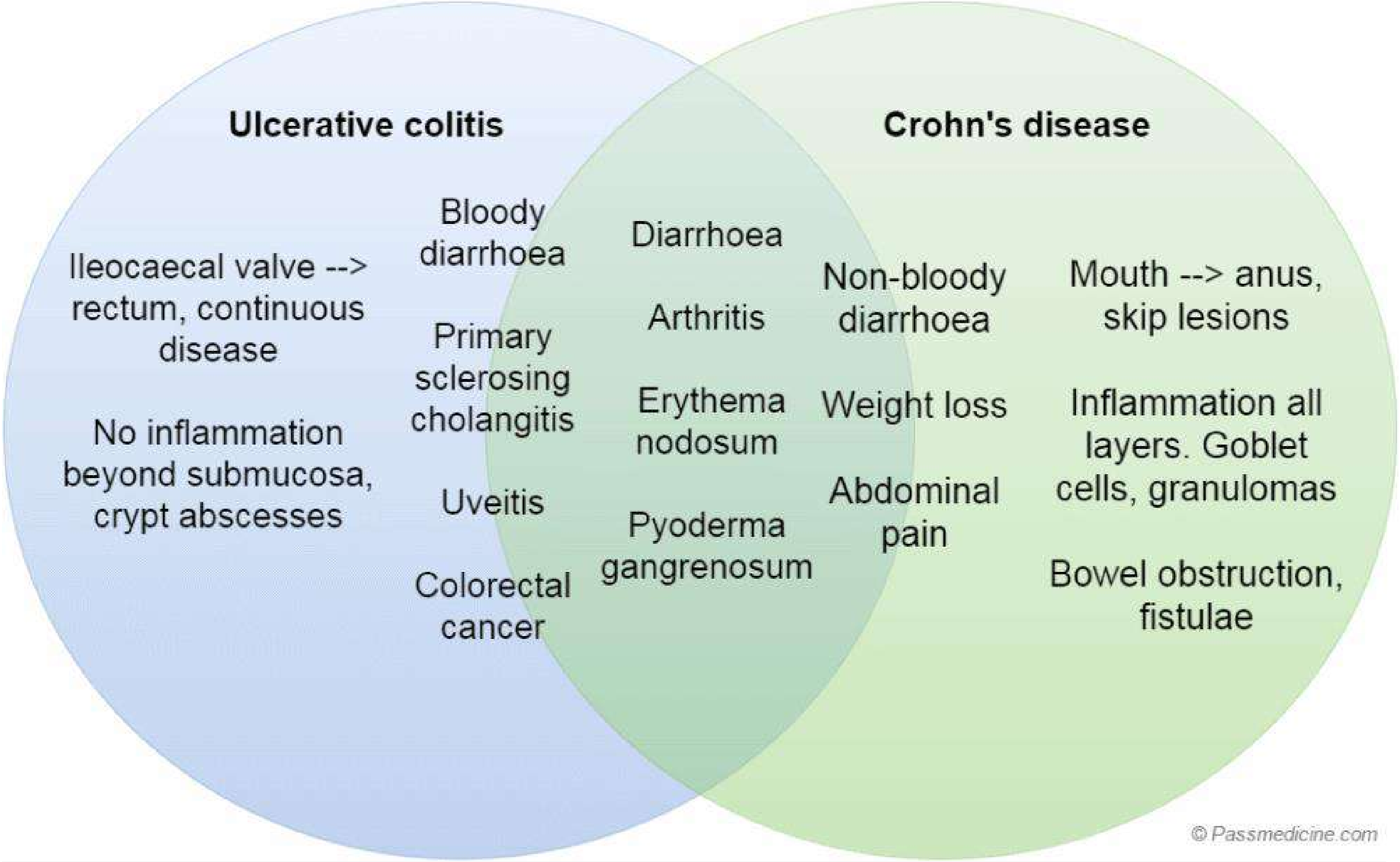
Ulcerative colitis (UC) is a form of inflammatory bowel disease. Inflammation always starts at rectum (hence it is the most common site for UC), never spreads beyond ileocaecal valve and is continuous. The peak incidence of ulcerative colitis is in people aged 15-25 years and in those aged 55-65 years.

The initial presentation is usually following insidious and intermittent symptoms. Features include:

- bloody diarrhoea
- urgency
- tenesmus
- abdominal pain, particularly in the left lower quadrant
- extra-intestinal features (see below)

Questions regarding the 'extra-intestinal' features of inflammatory bowel disease are common:

| | Common to both Crohn's disease (CD) and Ulcerative colitis (UC) | Notes |
|---|---|---|
| **Related to disease activity** | Arthritis: pauciarticular, asymmetric<br>Erythema nodosum<br>Episcleritis<br>Osteoporosis | Arthritis is the most common extra-intestinal feature in both CD and UC<br>Episcleritis is more common in CD |
| **Unrelated to disease activity** | Arthritis: polyarticular, symmetric<br>Uveitis<br>Pyoderma gangrenosum<br>Clubbing<br>Primary sclerosing cholangitis | Primary sclerosing cholangitis is much more common in UC<br>Uveitis is more common in UC |



Ulcerative colitis
Crohn's disease
Ileocaecal valve --> rectum, continuous disease
No inflammation beyond submucosa, crypt abscesses
Bloody diarrhoea
Primary sclerosing cholangitis
Uveitis
Colorectal cancer
Diarrhoea
Arthritis
Erythema nodosum
Pyoderma gangrenosum
Non-bloody diarrhoea
Weight loss
Abdominal pain
Mouth --> anus, skip lesions
Inflammation all layers. Goblet cells, granulomas
Bowel obstruction, fistulae
© Passmedicine.com

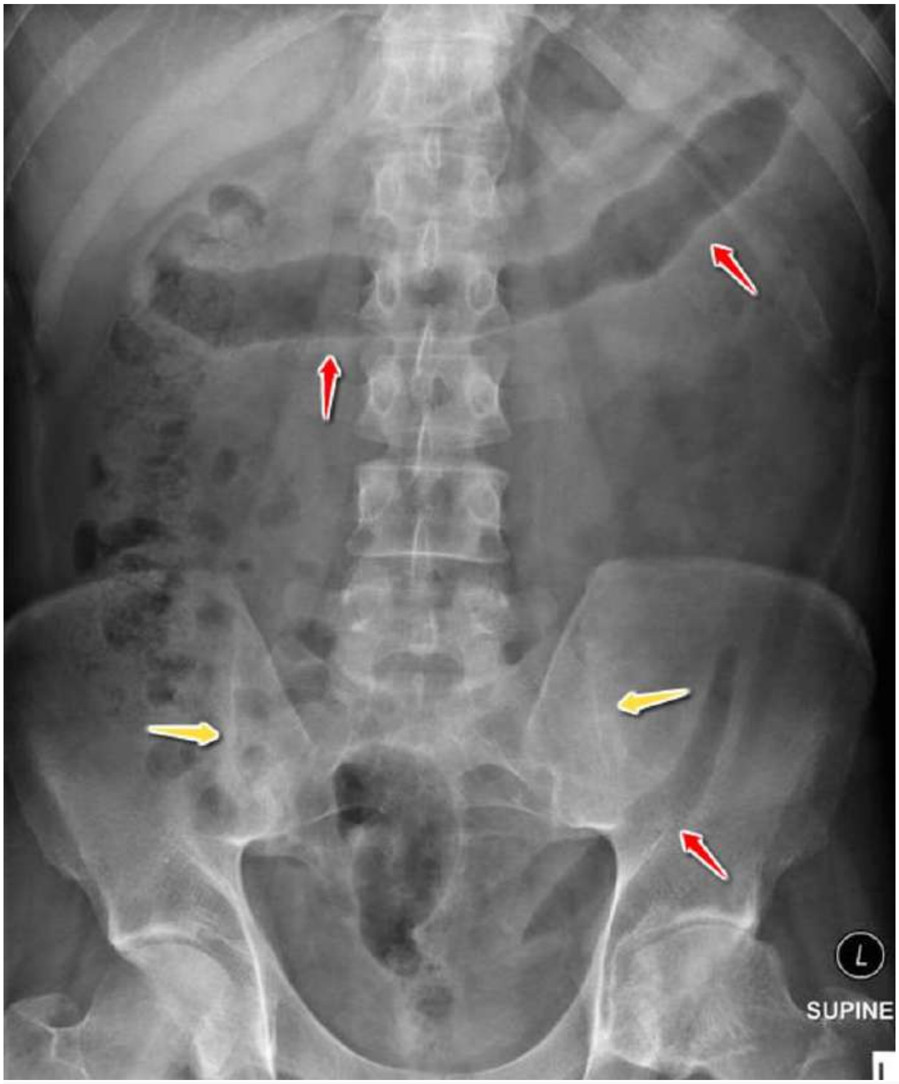
Venn diagram showing shared features and differences between ulcerative colitis and Crohn's disease. Note that whilst some features are present in both, some are much more common in one of the conditions, for example colorectal cancer in ulcerative colitis

Pathology

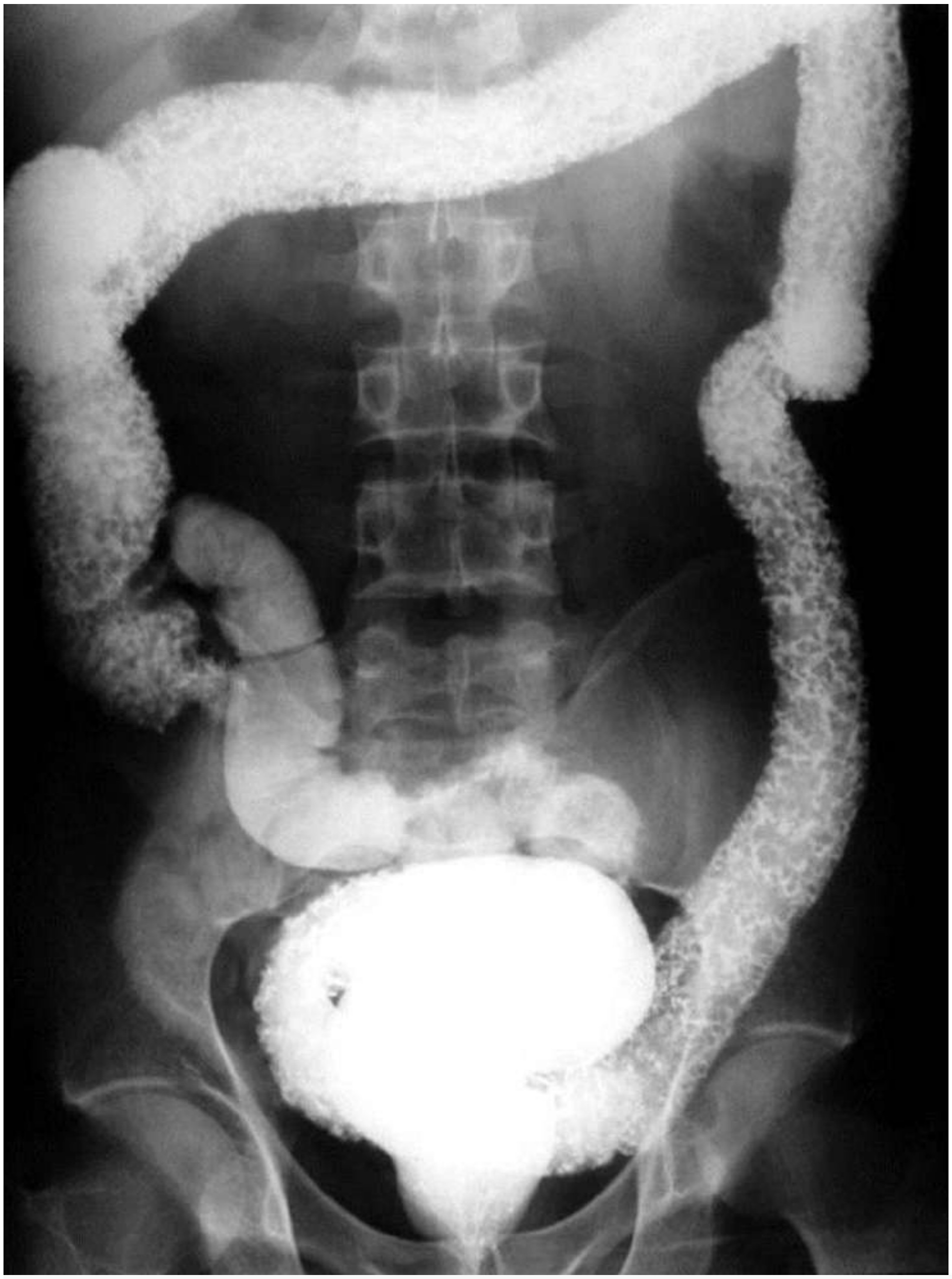
- red, raw mucosa, bleeds easily
- no inflammation beyond submucosa (unless fulminant disease)
- widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')
- inflammatory cell infiltrate in lamina propria
- neutrophils migrate through the walls of glands to form crypt abscesses
- depletion of goblet cells and mucin from gland epithelium
- granulomas are infrequent

Barium enema

- loss of haustrations
- superficial ulceration, 'pseudopolyps'
- long standing disease: colon is narrow and short -'drainpipe colon'



Abdominal x-ray from a patient with ulcerative colitis showing lead pipe appearance of the colon (red arrows). Ankylosis of the left sacroiliac joint and partial ankylosis on the right (yellow arrow), reinforcing the link with sacroilitis.



Barium enema from a patient with ulcerative colitis. The whole colon, without skips is affected by an irregular mucosa with loss of normal haustral markings.

## ULCERATIVE COLITIS: MANAGEMENT

Treatment can be divided into inducing and maintaining remission. NICE updated their guidelines on the management of ulcerative colitis in 2019.

The severity of UC is usually classified as being mild, moderate or severe:

- mild: < 4 stools/day, only a small amount of blood
- moderate: 4-6 stools/day, varying amounts of blood, no systemic upset
- severe: >6 bloody stools per day + features of systemic upset (pyrexia, tachycardia, anaemia, raised inflammatory markers)

**Inducing remission**

Treating mild-to-moderate ulcerative colitis

- proctitis
    - topical (rectal) aminosalicylate: for distal colitis rectal mesalazine has been shown to be superior to rectal steroids and oral aminosalicylates
    - if remission is not achieved within 4 weeks, add an oral aminosalicylate
    - if remission still not achieved add topical or oral corticosteroid
- proctosigmoiditis and left-sided ulcerative colitis
    - topical (rectal) aminosalicylate
    - if remission is not achieved within 4 weeks, add a high-dose oral aminosalicylate OR switch to a high-dose oral aminosalicylate and a topical corticosteroid
    - if remission still not achieved stop topical treatments and offer an oral aminosalicylate and an oral corticosteroid
- extensive disease
    - topical (rectal) aminosalicylate and a high-dose oral aminosalicylate:
    - if remission is not achieved within 4 weeks, stop topical treatments and offer a high-dose oral aminosalicylate and an oral corticosteroid

Severe colitis

- should be treated in hospital
- intravenous steroids are usually given first-line
    - intravenous ciclosporin may be used if steroid are contraindicated
- if after 72 hours there has been no improvement, consider adding intravenous ciclosporin to intravenous corticosteroids or consider surgery

**Maintaining remission**

Following a mild-to-moderate ulcerative colitis flare

- proctitis and proctosigmoiditis
    - topical (rectal) aminosalicylate alone (daily or intermittent) or
    - an oral aminosalicylate plus a topical (rectal) aminosalicylate (daily or intermittent) or
    - an oral aminosalicylate by itself: this may not be effective as the other two options
- left-sided and extensive ulcerative colitis
    - low maintenance dose of an oral aminosalicylate

Following a severe relapse or >=2 exacerbations in the past year

- oral azathioprine or oral mercaptopurine

Other points

- methotrexate is not recommended for the management of UC (in contrast to Crohn's disease)
- there is some evidence that probiotics may prevent relapse in patients with mild to moderate disease

# ULCERATIVE COLITIS: COLORECTAL CANCER

Overview
- risk of colorectal cancer is significantly higher than that of the general population although studies report widely varying rates
- the increased risk is mainly related to chronic inflammation
- worse prognosis than patients without ulcerative colitis (partly due to delayed diagnosis)
- lesions may be multifocal

Factors increasing risk of cancer
- disease duration > 10 years
- patients with pancolitis
- onset before 15 years old
- unremitting disease
- poor compliance to treatment

Colonoscopy surveillance in inflammatory bowel disease patients should be decided following risk stratification.

**Lower risk**
5 year follow up colonoscopy
- Extensive colitis with no active endoscopic/histological inflammation
- OR left sided colitis
- OR Crohn's colitis of <50% colon

**Intermediate risk**
3 year colonoscopy
- Extensive colitis with mild active endoscopy/histological inflammation
- OR post-inflammatory polyps
- OR family history of colorectal cancer in a first degree relative aged 50 or over

**Higher risk**
1 year follow up colonoscopy
- Extensive colitis with moderate/severe active endoscopic/histological inflammation
- OR stricture in past 5 years
- OR dysplasia in past 5 years declining surgery
- OR primary sclerosing cholangitis / transplant for primary sclerosing cholangitis
- OR family history of colorectal cancer in first degree relatives aged <50 years

# AMINOSALICYLATE DRUGS

5-aminosalicyclic acid (5-ASA) is released in the colon and is not absorbed. It acts locally as an anti-inflammatory. The mechanism of action is not fully understood but 5-ASA may inhibit prostaglandin synthesis

Sulphasalazine
- a combination of sulphapyridine (a sulphonamide) and 5-ASA
- many side-effects are due to the sulphapyridine moiety: rashes, oligospermia, headache, Heinz body anaemia, megaloblastic anaemia, lung fibrosis
- other side-effects are common to 5-ASA drugs (see mesalazine)

Mesalazine
- a delayed release form of 5-ASA
- sulphapyridine side-effects seen in patients taking sulphasalazine are avoided
- mesalazine is still however associated with side-effects such as GI upset, headache, agranulocytosis, pancreatitis*, interstitial nephritis

Olsalazine
- two molecules of 5-ASA linked by a diazo bond, which is broken by colonic bacteria

*pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine

# IRRITABLE BOWEL SYNDROME

NICE published clinical guidelines on the diagnosis and management of irritable bowel syndrome (IBS) in 2008

The diagnosis of IBS should be considered if the patient has had the following for at least 6 months:
- abdominal pain, and/or
- bloating, and/or
- change in bowel habit

A positive diagnosis of IBS should be made if the patient has abdominal pain relieved by defecation or associated with altered bowel frequency stool form, in addition to 2 of the following 4 symptoms:
- altered stool passage (straining, urgency, incomplete evacuation)
- abdominal bloating (more common in women than men), distension, tension or hardness
- symptoms made worse by eating
- passage of mucus

Features such as lethargy, nausea, backache and bladder symptoms may also support the diagnosis

Red flag features should be enquired about:
- rectal bleeding

- unexplained/unintentional weight loss
- family history of bowel or ovarian cancer
- onset after 60 years of age

Suggested primary care investigations are:
- full blood count
- ESR/CRP
- coeliac disease screen (tissue transglutaminase antibodies)

# IRRITABLE BOWEL SYNDROME: MANAGEMENT

The management of irritable bowel syndrome (IBS) is often difficult and varies considerably between patients. NICE updated it's guidelines in 2015.

First-line pharmacological treatment - according to predominant symptom
- pain: antispasmodic agents
- constipation: laxatives but avoid lactulose
- diarrhoea: loperamide is first-line

For patients with constipation who are not responding to conventional laxatives linaclotide may be considered, if:
- optimal or maximum tolerated doses of previous laxatives from different classes have not helped and
- they have had constipation for at least 12 months

Second-line pharmacological treatment
- low-dose tricyclic antidepressants (e.g. amitriptyline 5-10 mg) are used in preference to selective serotonin reuptake inhibitors

Other management options
- psychological interventions - if symptoms do not respond to pharmacological treatments after 12 months and who develop a continuing symptom profile (refractory IBS), consider referring for cognitive behavioural therapy, hypnotherapy or psychological therapy
- complementary and alternative medicines: 'do not encourage use of acupuncture or reflexology for the treatment of IBS'

General dietary advice
- have regular meals and take time to eat
- avoid missing meals or leaving long gaps between eating
- drink at least 8 cups of fluid per day, especially water or other non-caffeinated drinks such as herbal teas
- restrict tea and coffee to 3 cups per day

- reduce intake of alcohol and fizzy drinks
- consider limiting intake of high-fibre food (for example, wholemeal or high-fibre flour and breads, cereals high in bran, and whole grains such as brown rice)
- reduce intake of 'resistant starch' often found in processed foods
- limit fresh fruit to 3 portions per day
- for diarrhoea, avoid sorbitol
- for wind and bloating consider increasing intake of oats (for example, oat-based breakfast cereal or porridge) and linseeds (up to one tablespoon per day).

# LAXATIVES

Laxatives are one of the most commonly prescribed medicines in clinical practice. It should of course be remembered that constipation may be secondary to other pathology but many patients will have simple idiopathic constipation.

The BNF divides laxatives into the following groups:
- osmotic laxatives
- stimulant
- bulk-forming
- faecal softners

Osmotic laxatives
- examples include lactulose, macrogols and rectal phosphates

Stimulant laxatives
- examples include senna, docusate, bisacodyl and glycerol
- co-danthramer should only be prescribed to palliative patients due to its carcinogenic potential

Bulk-forming laxatives
examples include ispaghula husk and methylcellulose

Faecal softners
- include arachis oil enemas
- not commonly prescribed

# HAEMOCHROMATOSIS: FEATURES

Haemochromatosis is an autosomal recessive disorder of iron absorption and metabolism resulting in iron accumulation. It is caused by inheritance of mutations in the HFE gene on both copies of chromosome 6*. It is often asymptomatic in early disease and initial symptoms often non-specific e.g. lethargy and arthralgia

Epidemiology

- 1 in 10 people of European descent carry a mutation in the genes affecting iron metabolism, mainly HFE
- prevalence in people of European descent = 1 in 200, making it more common than cystic fibrosis

Presenting features

- early symptoms include fatigue, erectile dysfunction and arthralgia (often of the hands)
- 'bronze' skin pigmentation
- diabetes mellitus
- liver: stigmata of chronic liver disease, hepatomegaly, cirrhosis, hepatocellular deposition)
- cardiac failure (2nd to dilated cardiomyopathy)
- hypogonadism (2nd to cirrhosis and pituitary dysfunction - hypogonadotrophic hypogonadism)
- arthritis (especially of the hands)

Questions have previously been asked regarding which features are reversible with treatment:

| Reversible complications | Irreversible complications |
|---|---|
| • Cardiomyopathy<br>• Skin pigmentation | • Liver cirrhosis**<br>• Diabetes mellitus<br>• Hypogonadotrophic hypogonadism<br>• Arthropathy |

*there are rare cases of families with classic features of genetic haemochromatosis but no mutation in the HFE gene
**whilst elevated liver function tests and hepatomegaly may be reversible, cirrhosis is not

# HAEMOCHROMATOSIS: INVESTIGATION AND MANAGEMENT

Haemochromatosis is an autosomal recessive disorder of iron absorption and metabolism resulting in iron accumulation. It is caused by inheritance of mutations in the HFE gene on both copies of chromosome 6*.

There is continued debate about the best investigation to screen for haemochromatosis.

- general population: transferrin saturation is considered the most useful marker. Ferritin should also be measured but is not usually abnormal in the early stages of iron accumulation

- testing family members: genetic testing for HFE mutation

These guidelines may change as HFE gene analysis become less expensive

Diagnostic tests

- molecular genetic testing for the C282Y and H63D mutations
- liver biopsy: Perl's stain

Typical iron study profile in patient with haemochromatosis

- transferrin saturation > 55% in men or > 50% in women
- raised ferritin (e.g. > 500 ug/l) and iron
- low TIBC

Venesection is the first-line treatment

- monitoring adequacy of venesection: transferrin saturation should be kept below 50% and the serum ferritin concentration below 50 ug/l

Joint x-rays characteristically show chondrocalcinosis

*there are rare cases of families with classic features of genetic haemochromatosis but no mutation in the HFE gene

# HEPATOBILIARY DISEASE AND RELATED DISORDERS

The table below gives characteristic exam question features for conditions causing hepatobiliary disease and related disorders:

| Condition | Features |
|---|---|
| **Viral hepatitis** | Common symptoms include:<br>• nausea and vomiting, anorexia<br>• myalgia<br>• lethargy<br>• right upper quadrant (RUQ) pain<br>Questions may point to risk factors such as foreign travel or intravenous drug use. |
| **Congestive hepatomegaly** | The liver only usually causes pain if stretched. One common way this can occur is as a consequence of congestive heart failure. In severe cases cirrhosis may occur. |
| **Biliary colic** | RUQ pain, intermittent, usually begins abruptly and subsides gradually. Attacks often occur after eating. Nausea is common. |

| Condition | Features |
|---|---|
| | It is sometimes taught that patients are female, forties, fat and fair although this is obviously a generalisation. |
| **Acute cholecystitis** | Pain similar to biliary colic but more severe and persistent. The pain may radiate to the back or right shoulder.<br>The patient may be pyrexial and Murphy's sign positive (arrest of inspiration on palpation of the RUQ) |
| **Ascending cholangitis** | An infection of the bile ducts commonly secondary to gallstones. Classically presents with a triad of:<br>• fever (rigors are common)<br>• RUQ pain<br>• jaundice |
| **Gallstone ileus** | This describes small bowel obstruction secondary to an impacted gallstone. It may develop if a fistula forms between a gangrenous gallbladder and the duodenum.<br>Abdominal pain, distension and vomiting are seen. |
| **Cholangiocarcinoma** | Persistent biliary colic symptoms, associated with anorexia, jaundice and weight loss. A palpable mass in the right upper quadrant (Courvoisier sign), periumbilical lymphadenopathy (Sister Mary Joseph nodes) and left supraclavicular adenopathy (Virchow node) may be seen |
| **Acute pancreatitis** | Usually due to alcohol or gallstones<br>Severe epigastric pain<br>Vomiting is common<br>Examination may reveal tenderness, ileus and low-grade fever<br>Periumbilical discolouration (Cullen's sign) and flank discolouration (Grey-Turner's sign) is described but rare |
| **Pancreatic cancer** | Painless jaundice is the classical presentation of pancreatic cancer. However pain is actually a relatively common presenting symptom of pancreatic cancer. Anorexia and weight loss are common |
| **Amoebic liver abscess** | Typical symptoms are malaise, anorexia and weight loss. The associated RUQ pain tends to be mild and jaundice is uncommon. |

# HEPATITIS B SEROLOGY

Interpreting hepatitis B serology is a dying art form which still occurs at regular intervals in medical exams. It is important to remember a few key facts:

- surface antigen (HBsAg) is the first marker to appear and causes the production of anti-HBs
- HBsAg normally implies acute disease (present for 1-6 months)
- if HBsAg is present for > 6 months then this implies chronic disease (i.e. Infective)
- Anti-HBs implies immunity (either exposure or immunisation). It is negative in chronic disease

- Anti-HBc implies previous (or current) infection. IgM anti-HBc appears during acute or recent hepatitis B infection and is present for about 6 months. IgG anti-HBc persists
- HbeAg results from breakdown of core antigen from infected liver cells as is, therefore, a marker of infectivity

Example results
- previous immunisation: anti-HBs positive, all others negative
- previous hepatitis B (> 6 months ago), not a carrier: anti-HBc positive, HBsAg negative
- previous hepatitis B, now a carrier: anti-HBc positive, HBsAg positive

HBsAg = ongoing infection, either acute or chronic if present > 6 months

anti-HB**c** = **c**aught, i.e. negative if immunized

# HEPATITIS B AND PREGNANCY

Basics
- all pregnant women are offered screening for hepatitis B
- babies born to mothers who are chronically infected with hepatitis B or to mothers who've had acute hepatitis B during pregnancy should receive a complete course of vaccination + hepatitis B immunoglobulin
- studies are currently evaluating the role of oral antiviral treatment (e.g. Lamivudine) in the latter part of pregnancy
- there is little evidence to suggest caesarean section reduces vertical transmission rates
- hepatitis B cannot be transmitted via breastfeeding (in contrast to HIV)

# HEPATITIS D

Hepatitis D is a single stranded RNA virus that is transmitted parenterally. It is an incomplete RNA virus that requires hepatitis B surface antigen to complete its replication and transmission cycle.

It is transmitted in a similar fashion to hepatitis B (exchange of bodily fluids) and patients may be infected with hepatitis B and hepatitis D at the same time.

Hepatitis D terminology:
- Co-infection: Hepatitis B and Hepatitis D infection at the same time.
- Superinfection: A hepatitis B surface antigen positive patient subsequently develops a hepatitis D infection.

Superinfection is associated with high risk of fulminant hepatitis, chronic hepatitis status and cirrhosis.

Diagnosis is made via reverse polymerase chain reaction of hepatitis D RNA. Interferon is currently used as treatment, but with a poor evidence base.

## AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is condition of unknown aetiology which is most commonly seen in young females. Recognised associations include other autoimmune disorders, hypergammaglobulinaemia and HLA B8, DR3. Three types of autoimmune hepatitis have been characterised according to the types of circulating antibodies present

| Type I | Type II | Type III |
|---|---|---|
| Anti-nuclear antibodies (ANA) and/or anti-smooth muscle antibodies (SMA)<br>Affects both adults and children | Anti-liver/kidney microsomal type 1 antibodies (LKM1)<br>Affects children only | Soluble liver-kidney antigen<br>Affects adults in middle-age |

Features

- may present with signs of chronic liver disease
- acute hepatitis: fever, jaundice etc (only 25% present in this way)
- amenorrhoea (common)
- ANA/SMA/LKM1 antibodies, raised IgG levels
- liver biopsy: inflammation extending beyond limiting plate 'piecemeal necrosis', bridging necrosis

Management

- steroids, other immunosuppressants e.g. azathioprine
- liver transplantation

## GILBERT'S SYNDROME

Gilbert's syndrome is an autosomal recessive* condition of defective bilirubin conjugation due to a deficiency of UDP glucuronosyltransferase. The prevalence is approximately 1-2% in the general population.

Features

- unconjugated hyperbilirubinaemia (i.e. not in urine)
- jaundice may only be seen during an intercurrent illness, exercise or fasting

Investigation and management

- investigation: rise in bilirubin following prolonged fasting or IV nicotinic acid

- no treatment required

*the exact mode of inheritance is still a matter of debate

# DUBIN-JOHNSON SYNDROME

Dubin-Johnson syndrome is a benign autosomal recessive disorder resulting in hyperbilirubinaemia (conjugated, therefore present in urine). It is due to a defect in the canillicular multispecific organic anion transporter (cMOAT) protein. This causes defective hepatic bilirubin excretion

# ISCHAEMIC HEPATITIS

Ischaemic hepatitis is a diffuse hepatic injury resulting from acute hypoperfusion (sometimes known as 'shock liver'). It is not an inflammatory process. It is diagnosed in the presence of an inciting event (e.g. a cardiac arrest) and marked increases in aminotransferase levels (exceeding 1000 international unit/L or 50 times the upper limit of normal). Often, it will occur in conjunction with acute kidney injury (tubular necrosis) or other end-organ dysfunction.

# LIVER CIRRHOSIS

Liver cirrhosis remains a significant problem in the developed world, account for 60,000 deaths in the UK each year.

Causes:
- alcohol
- non-alcoholic fatty liver disease (NAFLD)
- viral hepatitis (B and C)

Diagnosis
- traditionally a liver biopsy was used. This procedure is however associated with adverse effects such as bleeding and pain
- other techniques such as transient elastography and acoustic radiation force impulse imaging are increasingly used and were recommended by NICE in their 2016 guidelines
- for patients with NAFLD, NICE recommend using the enhanced liver fibrosis score to screen for patients who need further testing

What is transient elastography?
- brand name 'Fibroscan'

- uses a 50-MHz wave is passed into the liver from a small transducer on the end of an ultrasound probe
- measures the 'stiffness' of the liver which is a proxy for fibrosis

- In terms of screening for cirrhosis NICE made a specific recommendation, suggesting to offer transient elastography to:
- people with hepatitis C virus infection
- men who drink over 50 units of alcohol per week and women who drink over 35 units of alcohol per week and have done so for several months
- people diagnosed with alcohol-related liver disease

Further investigations

- NICE recommend doing an upper endoscopy to check for varices in patient's with a new diagnosis of cirrhosis
- liver ultrasound every 6 months (+/- alpha-feto protein) to check for hepatocellular cancer

# SCORING SYSTEMS FOR LIVER CIRRHOSIS

For many years the **Child-Pugh** classification was used to classify the severity of liver cirrhosis. However, in recent years the **Model for End-Stage Liver Disease (MELD)** has been increasingly used, particularly patient's who are on a liver transplant waiting list

**Child-Pugh classification**

| Score | 1 | 2 | 3 |
|---|---|---|---|
| Bilirubin (μmol/l) | <34 | 34-50 | >50 |
| Albumin (g/l) | >35 | 28-35 | <28 |
| Prothrombin time, prolonged by (s) | <4 | 4-6 | >6 |
| Encephalopathy | none | mild | marked |
| Ascites | none | mild | marked |

Summation of the scores allows the severity to be graded either A, B or C:

- < 7 = A
- 7-9 = B
- > 9 = C

**MELD**

Uses a combination of a patient's bilirubin, creatinine, and the international normalized ratio (INR) to predict survival. A formula is used to calculate the score:

$$\text{MELD} = 3.78 \times \ln[\text{serum bilirubin (mg/dL)}] + 11.2 \times \ln[\text{INR}] + 9.57 \times \ln[\text{serum creatinine (mg/dL)}] + 6.43$$

The 3-month mortality based on MELD scores:

- 40 or more: 71.3% mortality
- 30 - 39: 52.6% mortality
- 20 - 29: 19.6% mortality
- 10 - 19: 6.0% mortality
- < 9: 1.9% mortality

# ASCITES

The causes of ascites can be grouped into those with a serum-ascites albumin gradient (SAAG) <11 g/L or a gradient >11g/L as per the table below:

| SAAG > 11g/L | SAAG <11g/L |
|---|---|
| **Indicates portal hypertension**<br><br>Cirrhosis<br>Alcoholic hepatitis<br>Cardiac ascites<br>Mixed ascites<br>Massive liver metastases<br>Fulminant hepatic failure<br>Budd-Chiari syndrome<br>Portal vein thrombosis<br>Veno-occlusive disease<br>Myxoedema<br>Fatty liver of pregnancy | Peritoneal carcinomatosis<br>Tuberculous peritonitis<br>Pancreatic ascites<br>Bowel obstruction<br>Biliary ascites<br>Postoperative lymphatic leak<br>Serositis in connective tissue diseases |

Management

- reducing dietary sodium
- fluid restriction is sometimes recommended if the sodium is < 125 mmol/L
- aldosterone antagonists: e.g. spironolactone
    - loop diuretics are often added. Some authorities only add loop diuretics in patients who don't respond to aldosterone agonists whereas other authorities suggest starting both types of diuretic on the first presentation of ascites
- drainage if tense ascites (therapeutic abdominal paracentesis)
    - large-volume paracentesis for the treatment of ascites requires albumin 'cover'. Evidence suggests this reduces paracentesis-induced circulatory dysfunction and mortality
    - paracentesis induced circulatory dysfunction can occur due to large volume paracentesis (> 5 litres). It is associated with a high rate of ascites recurrence, development of hepatorenal syndrome, dilutional hyponatraemia, and high mortality rate
- prophylactic antibiotics to reduce the risk of spontaneous bacterial peritonitis. NICE recommend: *'Offer prophylactic oral ciprofloxacin or norfloxacin for people with cirrhosis and ascites with an ascitic protein of 15 g/litre or less, until the ascites has resolved'*

- a transjugular intrahepatic portosystemic shunt (TIPS) may be considered in some patients

# SPONTANEOUS BACTERIAL PERITONITIS

Spontaneous bacterial peritonitis (SBP) is a form of peritonitis usually seen in patients with ascites secondary to liver cirrhosis.

Features
- ascites
- abdominal pain
- fever

Diagnosis
- paracentesis: neutrophil count > 250 cells/ul
- the most common organism found on ascitic fluid culture is E. coli

Management
- intravenous cefotaxime is usually given

Antibiotic prophylaxis should be given to patients with ascites if:
- patients who have had an episode of SBP
- patients with fluid protein <15 g/l and either Child-Pugh score of at least 9 or hepatorenal syndrome
- NICE recommend: *'Offer prophylactic oral ciprofloxacin or norfloxacin for people with cirrhosis and ascites with an ascitic protein of 15 g/litre or less until the ascites has resolved'*

Alcoholic liver disease is a marker of poor prognosis in SBP.

# HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the third most common cause of cancer worldwide. Chronic hepatitis B is the most common cause of HCC worldwide with chronic hepatitis C being the most common cause in Europe.

The main risk factor for developing HCC is liver cirrhosis, for example secondary* to hepatitis B & C, alcohol, haemochromatosis and primary biliary cirrhosis. Other risk factors include:
- alpha-1 antitrypsin deficiency
- hereditary tyrosinosis
- glycogen storage disease
- aflatoxin
- drugs: oral contraceptive pill, anabolic steroids

- porphyria cutanea tarda
- male sex
- diabetes mellitus, metabolic syndrome

Features
- tends to present late
- features of liver cirrhosis or failure may be seen: jaundice, ascites, RUQ pain, hepatomegaly, pruritus, splenomegaly
- possible presentation is decompensation in a patient with chronic liver disease
- raised AFP

Screening with ultrasound (+/- alpha-fetoprotein) should be considered for high risk groups such as:
- patients liver cirrhosis secondary to hepatitis B & C or haemochromatosis
- men with liver cirrhosis secondary to alcohol

Management options
- early disease: surgical resection
- liver transplantation
- radiofrequency ablation
- transarterial chemoembolisation
- sorafenib: a multikinase inhibitor

*Wilson's disease is an exception

# LIVER BIOPSY

Contraindications to percutaneous liver biopsy
- deranged clotting (e.g. INR > 1.4)
- low platelets (e.g. < 60 * 109/l)
- anaemia
- extrahepatic biliary obstruction
- hydatid cyst
- haemoangioma
- uncooperative patient
- ascites

# ASCENDING CHOLANGITIS

Ascending cholangitis is a bacterial infection (typically E. coli) of the biliary tree. The most common predisposing factor is gallstones.

Charcot's triad of right upper quadrant (RUQ) pain, fever and jaundice occurs in about 20-50% of patients

- fever is the most common feature, seen in 90% of patients
- RUQ pain 70%
- jaundice 60%
- hypotension and confusion are also common (the additional 2 factors in addition to the 3 above make Reynolds' pentad)

Other features

- raised inflammatory markers

Management

- intravenous antibiotics
- endoscopic retrograde cholangiopancreatography (ERCP) after 24-48 hours to relieve any obstruction

# PRIMARY BILIARY CHOLANGITIS

Primary biliary cholangitis (previously referred to as primary biliary cirrhosis) is a chronic liver disorder typically seen in middle-aged females (female:male ratio of 9:1). The aetiology is not fully understood although it is thought to be an autoimmune condition. Interlobular bile ducts become damaged by a chronic inflammatory process causing progressive cholestasis which may eventually progress to cirrhosis. The classic presentation is itching in a middle-aged woman

Associations

- Sjogren's syndrome (seen in up to 80% of patients)
- rheumatoid arthritis
- systemic sclerosis
- thyroid disease

Diagnosis

- anti-mitochondrial antibodies (AMA) M2 subtype are present in 98% of patients and are highly specific
- smooth muscle antibodies in 30% of patients
- raised serum IgM

Management

- pruritus: cholestyramine
- fat-soluble vitamin supplementation
- ursodeoxycholic acid

- liver transplantation e.g. if bilirubin > 100 (PBC is a major indication) - recurrence in graft can occur but is not usually a problem

Complications
- cirrhosis
- osteomalacia and osteoporosis
- significantly increased risk of hepatocellular carcinoma

## PRIMARY SCLEROSING CHOLANGITIS

Primary sclerosing cholangitis is a biliary disease of unknown aetiology characterised by inflammation and fibrosis of intra and extra-hepatic bile ducts.

Associations
- ulcerative colitis: 4% of patients with UC have PSC, 80% of patients with PSC have UC
- Crohn's (much less common association than UC)
- HIV

Features
- cholestasis
  - jaundice, pruritus
  - raised bilirubin + ALP
- right upper quadrant pain
- fatigue

Investigation
- endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) are the standard diagnostic investigations, showing multiple biliary strictures giving a 'beaded' appearance
- p-ANCA may be positive
- there is a limited role for liver biopsy, which may show fibrous, obliterative cholangitis often described as 'onion skin'

Complications
- cholangiocarcinoma (in 10%)
- increased risk of colorectal cancer

## HEPATOMEGALY

Common causes of hepatomegaly

- Cirrhosis: if early disease, later liver decreases in size. Associated with a non-tender, firm liver
- Malignancy: metastatic spread or primary hepatoma. Associated with a hard, irregular. liver edge
- Right heart failure: firm, smooth, tender liver edge. May be pulsatile

Other causes
- viral hepatitis
- glandular fever
- malaria
- abscess: pyogenic, amoebic
- hydatid disease
- haematological malignancies
- haemochromatosis
- primary biliary cirrhosis
- sarcoidosis, amyloidosis

# HEPATOSPLENOMEGALY

Causes of hepatosplenomegaly
- chronic liver disease* with portal hypertension
- infections: glandular fever, malaria, hepatitis
- lymphoproliferative disorders
- myeloproliferative disorders e.g. CML
- amyloidosis

*the latter stages of cirrhosis are associated with a small liver

# HEPATORENAL SYNDROME: MANAGEMENT

The management of hepatorenal syndrome (HRS) is notoriously difficult. The ideal treatment is liver transplantation but patients are often too unwell to have surgery and there is a shortage of donors

The most accepted theory regarding the pathophysiology of HRS is that vasoactive mediators cause **splanchnic vasodilation** which in turn reduces the systemic vascular resistance. This results in 'underfilling' of the kidneys. This is sensed by the juxtaglomerular apparatus which then activates the renin-angiotensin-aldosterone system, causing renal vasoconstriction which is not enough to counterbalance the effects of the splanchnic vasodilation.

Hepatorenal syndrome has been categorized into two types:

| Type 1 HRS | Type 2 HRS |
|---|---|
| Rapidly progressive<br>Doubling of serum creatinine to > 221 µmol/L or a halving of the creatinine clearance to less than 20 ml/min over a period of less than 2 weeks<br>Very poor prognosis | Slowly progressive<br>Prognosis poor, but patients may live for longer |

Management options
vasopressin analogues, for example terlipressin, have a growing evidence base supporting their use. They work by causing vasoconstriction of the splanchnic circulation
volume expansion with 20% albumin
transjugular intrahepatic portosystemic shunt

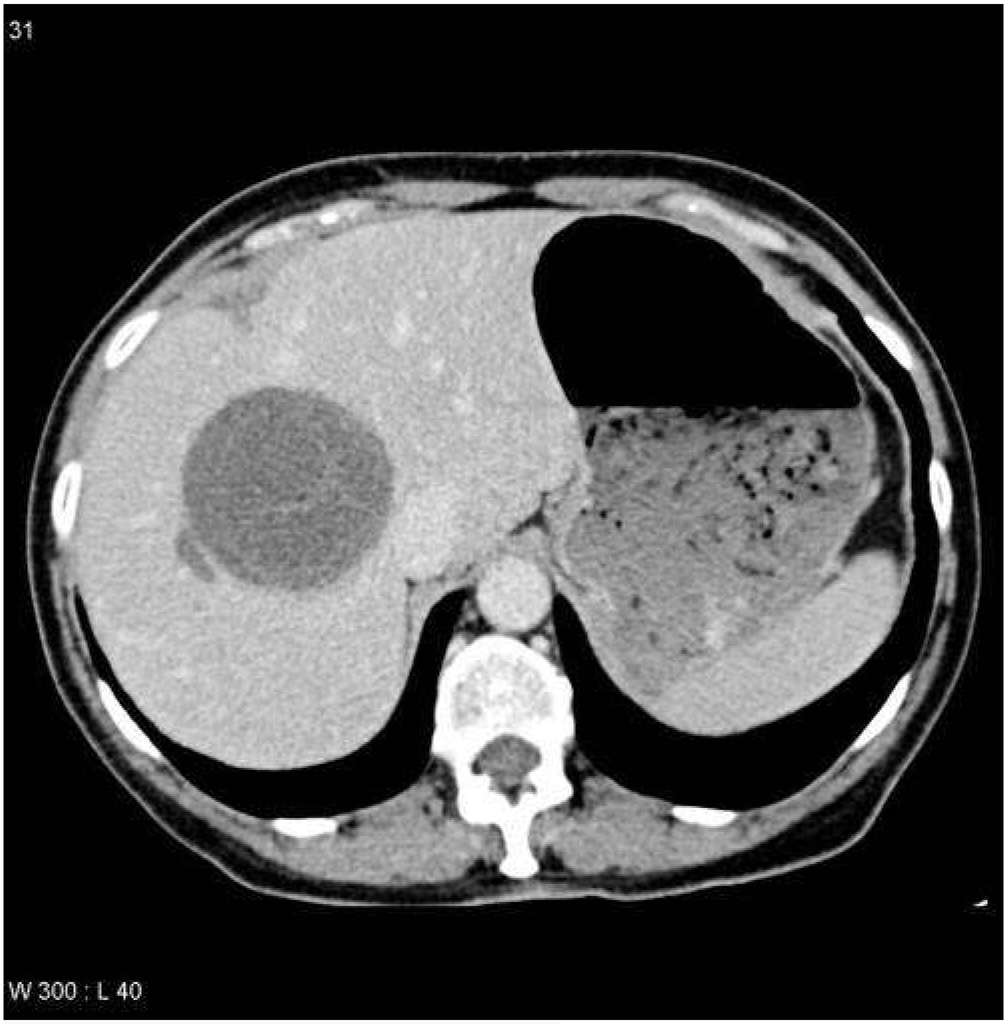
# HYDATID CYSTS

Hydatid cysts are endemic in Mediterranean and Middle Eastern countries. They are caused by the tapeworm parasite Echinococcus granulosus. An outer fibrous capsule is formed containing multiple small daughter cysts. These cysts are allergens which precipitate a type 1 hypersensitivity reaction.

Clinical features are as follows:

- Up to 90% cysts occur in the liver and lungs
- Can be asymtomatic, or symptomatic if cysts > 5cm in diameter
- Morbidity caused by cyst bursting, infection and organ dysfunction (biliary, bronchial, renal and cerebrospinal fluid outflow obstruction)
- In biliary ruputure there may be the classical triad of; biliary colic, jaundice, and urticaria

CT is the best investigation to differentiate hydatid cysts from amoebic and pyogenic cysts.
Surgery is the mainstay of treatment (the cyst walls must not be ruptured during removal and the contents sterilised first).



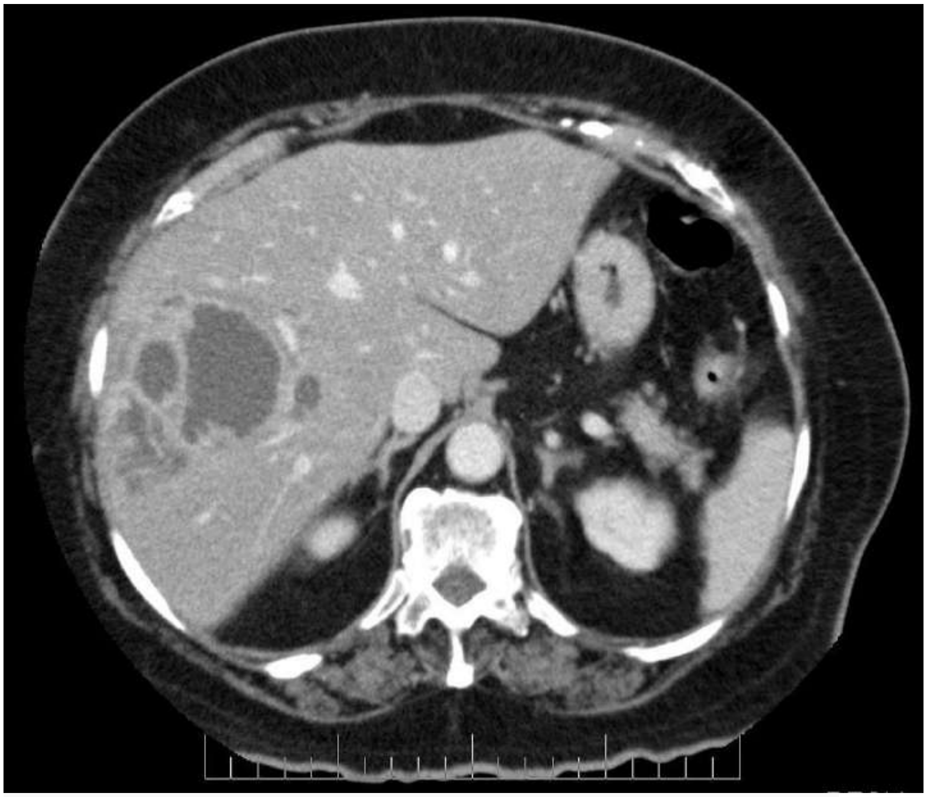
CT scan showing a hydatid cyst of the liver.

# PYOGENIC LIVER ABSCESS

The most common organisms found in pyogenic liver abscesses are Staphylococcus aureus in children and Escherichia coli in adults.

Management

- drainage (typically percutaneous) and antibiotics
- amoxicillin + ciprofloxacin + metronidazole
- if penicillin allergic: ciprofloxacin + clindamycin



CT showing a pyogenic liver abscess in the right lobe of the liver.

## HIV: BILIARY AND PANCREATIC DISEASE

The most common cause of biliary disease in patients with HIV is sclerosing cholangitis due to infections such as CMV, Cryptosporidium and Microsporidia

Pancreatitis in the context of HIV infection may be secondary to anti-retroviral treatment (especially didanosine) or by opportunistic infections e.g. CMV

## VILLOUS ADENOMA

Villous adenomas are colonic polyps with the potential for malignant transformation. They characteristically secrete large amounts of mucous, potentially resulting in electrolyte disturbances.

The vast majority are asymptomatic. Possible features:

- non-specific lower gastrointestinal symptoms
- secretory diarrhoea may occur
- microcytic anaemia
- hypokalaemia

# PEUTZ-JEGHERS SYNDROME

Peutz-Jeghers syndrome is an autosomal dominant condition characterised by numerous hamartomatous polyps in the gastrointestinal tract. It is also associated with pigmented freckles on the lips, face, palms and soles. Although the polyps themselves don't have malignant potential, around 50% of patients will have died from another gastrointestinal tract cancer by the age of 60 years.

Genetics

- autosomal dominant
- responsible gene encodes serine threonine kinase LKB1 or STK11

Features

- hamartomatous polyps in GI tract (mainly small bowel)
- pigmented lesions on lips, oral mucosa, face, palms and soles
- intestinal obstruction e.g. intussusception
- gastrointestinal bleeding

Management

- conservative unless complications develop

# COLORECTAL CANCER

Colorectal cancer is the third most common type of cancer in the UK and the second most cause of cancer deaths. Annually there are about 150,000 new cases diagnosed and 50,000 deaths from the disease.

Location of cancer (averages)

- rectal: 40%
- sigmoid: 30%
- descending colon: 5%
- transverse colon: 10%
- ascending colon and caecum: 15%

# COLORECTAL CANCER: GENETICS

It is currently thought there are three types of colon cancer:

- sporadic (95%)
- hereditary non-polyposis colorectal carcinoma (HNPCC, 5%)
- familial adenomatous polyposis (FAP, <1%)

Studies have shown that sporadic colon cancer may be due to a series of genetic mutations. For example, more than half of colon cancers show allelic loss of the APC gene. It is believed a further series of gene abnormalities e.g. activation of the K-ras oncogene, deletion of p53 and DCC tumour suppressor genes lead to invasive carcinoma

HNPCC, an autosomal dominant condition, is the most common form of inherited colon cancer. Around 90% of patients develop cancers, often of the proximal colon, which are usually poorly differentiated and highly aggressive. Currently seven mutations have been identified, which affect genes involved in DNA mismatch repair leading to microsatellite instability. The most common genes involved are:

- MSH2 (60% of cases)
- MLH1 (30%)

Patients with HNPCC are also at a higher risk of other cancers, with endometrial cancer being the next most common association, after colon cancer.

The Amsterdam criteria are sometimes used to aid diagnosis:

- at least 3 family members with colon cancer
- the cases span at least two generations
- at least one case diagnosed before the age of 50 years

FAP is a rare autosomal dominant condition which leads to the formation of hundreds of polyps by the age of 30-40 years. Patients inevitably develop carcinoma. It is due to a mutation in a tumour suppressor gene called adenomatous polyposis coli gene (APC), located on chromosome 5. Genetic testing can be done by analysing DNA from a patient's white blood cells. Patients generally have a total colectomy with ileo-anal pouch formation in their twenties.

Patients with FAP are also at risk from duodenal tumours. A variant of FAP called Gardner's syndrome can also feature osteomas of the skull and mandible, retinal pigmentation, thyroid carcinoma and epidermoid cysts on the skin

# COLORECTAL CANCER: REFERRAL GUIDELINES

- NICE updated their referral guidelines in 2015. The following patients should be referred urgently (i.e. within 2 weeks) to colorectal services for investigation:
- patients >= 40 years with unexplained weight loss **AND** abdominal pain
- patients >= 50 years with unexplained rectal bleeding
- patients >= 60 years with iron deficiency anaemia **OR** change in bowel habit
- tests show occult blood in their faeces (see below)

An urgent referral (within 2 weeks) should be 'considered' if:

- there is a rectal or abdominal mass
- there is an unexplained anal mass or anal ulceration
- patients < 50 years with rectal bleeding AND any of the following unexplained symptoms/findings:
- -→ abdominal pain
- -→ change in bowel habit
- -→ weight loss
- -→ iron deficiency anaemia

**Faecal Occult Blood Testing (FOBT)**

This was one of the main changes in 2015. Remember that the NHS now has a national screening programme offering screening every 2 years to all men and women aged 60 to 74 years. Patients aged over 74 years may request screening.

In addition FOBT should be offered to:
patients >= 50 years with unexplained abdominal pain **OR** weight loss
patients < 60 years with changes in their bowel habit **OR** iron deficiency anaemia
patients >= 60 years who have anaemia even in the absence of iron deficiency

# COLORECTAL CANCER: SCREENING

Overview
- most cancers develop from adenomatous polyps. Screening for colorectal cancer has been shown to reduce mortality by 16%
- the NHS offers home-based, **Faecal Immunochemical Test (FIT)** screening to older adults
- another type of screening is also being rolled out - a **one-off flexible sigmoidoscopy**

**Faecal Immunochemical Test (FIT) screening**

Key points
- the NHS now has a national screening programme offering screening every 2 years to all men and women aged 60 to 74 years in England, 50 to 74 years in Scotland. Patients aged over 74 years may request screening
- eligible patients are sent Faecal Immunochemical Test (FIT) tests through the post
- a type of faecal occult blood (FOB) test which uses antibodies that specifically recognise human haemoglobin (Hb)
- used to detect, and can quantify, the amount of human blood in a single stool sample
- advantages over conventional FOB tests is that it only detects human haemoglobin, as opposed to animal haemoglobin ingested through diet
- only one faecal sample is needed compared to the 2-3 for conventional FOB tests

- whilst a numerical value is generated, this is not reported to the patient or GP, who will instead be informed if the test is normal or abnormal
- patients with abnormal results are offered a colonoscopy

At colonoscopy, approximately:
- 5 out of 10 patients will have a normal exam
- 4 out of 10 patients will be found to have polyps which may be removed due to their premalignant potential
- 1 out of 10 patients will be found to have cancer

**Flexible sigmoidoscopy screening**

Key points
- screening for bowel cancer using sigmoidoscopy is being rolled out as part of the NHS screening program
- the aim (other than to detect asymptomatic cancers) is to allow the detection and treatment of polyps, reducing the future risk of colorectal cancer
- this is being offered to people who are 55-years-old
- NHS patient information leaflets refer to this as 'bowel scope screening'
- patients can self-refer for bowel screening with sigmoidoscopy up to the age of 60, if the offer of routine one-off screening at age 55 had not been taken up

# CLOSTRIDIUM DIFFICILE

Clostridium difficile is a Gram positive rod often encountered in hospital practice. It produces an exotoxin which causes intestinal damage leading to a syndrome called pseudomembranous colitis. Clostridium difficile develops when the normal gut flora are suppressed by broad-spectrum antibiotics. Clindamycin is historically associated with causing Clostridium difficile but the aetiology has evolved significantly over the past 10 years. Second and third generation cephalosporins are now the leading cause of Clostridium difficile.

Other than antibiotics, risk factors include:
- proton pump inhibitors

Features
- diarrhoea
- abdominal pain
- a **raised white blood cell count** is characteristic
- if severe toxic megacolon may develop

Diagnosis
- is made by detecting Clostridium difficile **toxin** (CDT) in the stool

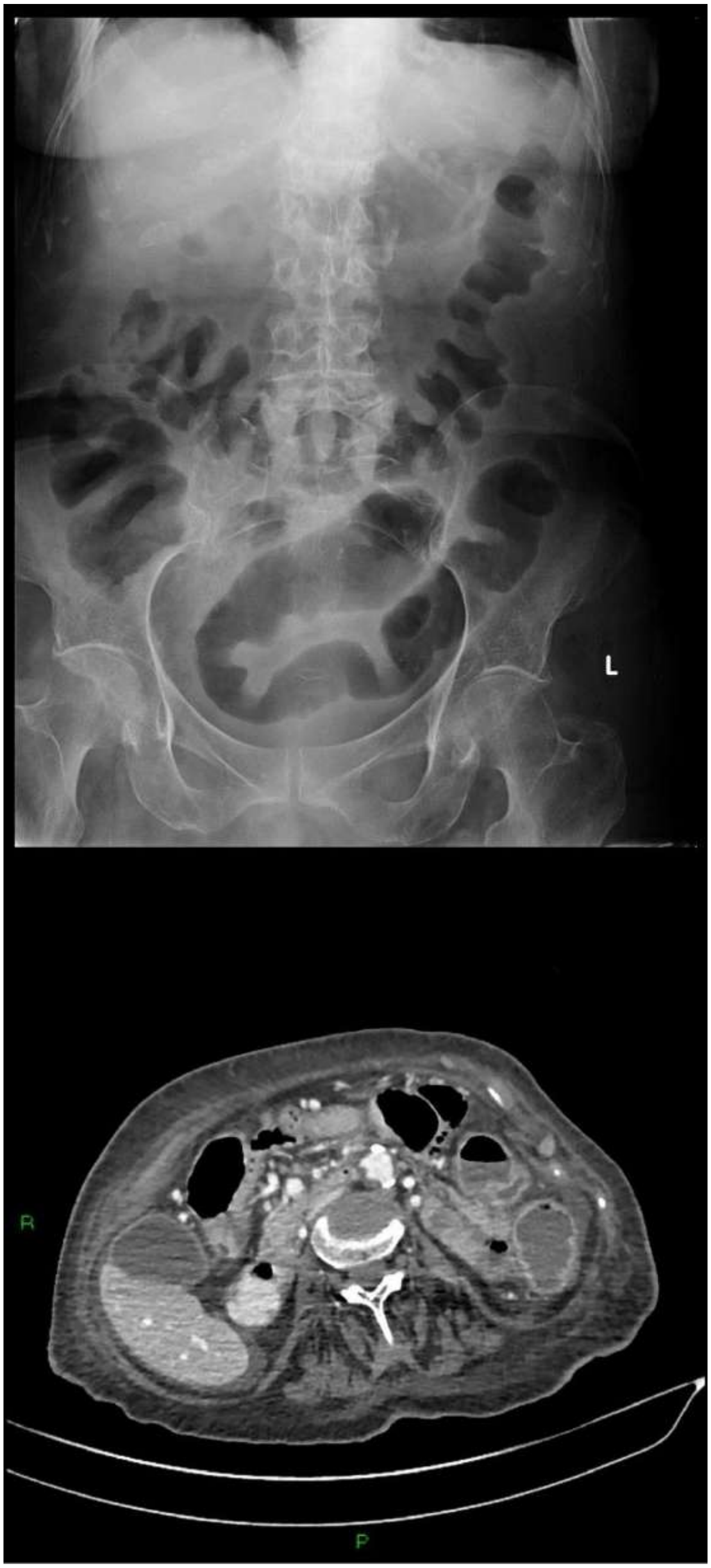
- Clostridium difficile **antigen** positivity only shows exposure to the bacteria, rather than current infection

Management

- first-line therapy is oral metronidazole for 10-14 days
- if severe or not responding to metronidazole then oral vancomycin may be used
- fidaxomicin may also be used for patients who are not responding , particularly those with multiple co-morbidities
- for life-threatening infections a combination of oral vancomycin and intravenous metronidazole should be used

Other therapies

- bezlotoxumab is a monoclonal antibody which targets Clostridium difficile toxin B - it is not in widespread use



Elderly lady with infectious colitis secondary to *Clostridium difficile*. On the abdominal film note the loss of bowel wall architecture and thumb-printing consistent with colitis. The CT from the same patient is enhanced by oral contrast. There is moderate free fluid in pelvis and peritoneum. The colon is oedematous throughout with enhancing walls, but of normal calibre. The sigmoid colon is smooth and featureless. Small bowel, liver, spleen, kidneys, adrenals and pancreas are normal.

# MELANOSIS COLI

Melanosis coli is a disorder of pigmentation of the bowel wall. Histology demonstrates pigment-laden macrophages

It is associated with laxative abuse, especially anthraquinone compounds such as senna

# ANAL CANCER

Anal cancer is defined as a malignancy which lies exclusively in the anal canal, the borders of which are the anorectal junction and the anal margin (area of pigmented skin surrounding the anal orifice). 80% of anal cancers are squamous cell carcinomas (SSCs). Other types include melanomas, lymphomas, and adenocarcinomas. The lymphatic drainage, and therefore, tumour spread, varies in different parts of the canal: anal margin tumours spread to the inguinal lymph nodes and those which are more proximal spread to the pelvic lymph nodes.

Epidemiology

- Anal cancer is relatively rare, with an annual incidence in the UK of about 1.5 in 100,000. However, its incidence is rising, especially amongst men who have sex with men, due to widespread infection by human papillomavirus (HPV).2
- 1:2 male:female ratio.3
- The average age of presentation in the UK is 85-89 years.
- 30-40% of patients present with lymph node involvement at diagnosis, however, distant spread is uncommon, with 5-8% of cases presenting with extrapelvic metastases at time of diagnosis.1

Risk factors

- HPV infection causes 80-85% of SSCs of the anus (usually HPV16 or HPV18 subtypes).
- Anal intercourse and a high lifetime number of sexual partners increases the risk of HPV infection.
- Men who have sex with men have a higher risk of anal cancer.
- Those with HIV and those taking immunosuppressive medication for HIV are at a greater risk of anal carcinoma.
- Women with a history of cervical cancer or cervical intraepithelial neoplasia (CIN) are also at greater risk of anal cancer.
- Immunosuppressive drugs used in transplant recipients increase the risk of anal cancer.
- Smoking is also a risk factor.

Patients typically present with a subacute onset of:

- Perianal pain, perianal bleeding
- A palpable lesion

- Faecal incontinence
- A neglected tumour in a female may present with a rectovaginal fistula.

Investigations
- T stage assessment: examination, including a digital rectal examination, anoscopic examination with biopsy, and palpation of the inguinal nodes.
- Imaging modalities: CT, MRI, endo-anal ultrasound and PET.
- The patient should be tested for relevant infections, including HIV.

T staging
The following is a T stage system for anal cancer described by the American Joint Committee on Cancer and the International Union Against Cancer:

| | |
|---|---|
| TX | primary tumour cannot be assessed |
| T0 | no evidence of primary tumour |
| Tis | carcinoma in situ |
| T1 | tumour 2 cm or less in greatest dimension |
| T2 | tumour more than 2 cm but not more than 5 cm in greatest dimension |
| T3 | tumour more than 5 cm in greatest dimension |
| T4 | tumour of any size that invades adjacent organ(s) - for example, vagina, urethra, bladder (direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) - is not classified as T4) |

# ANAL FISSURE

Anal fissures are longitudinal or elliptical tears of the squamous lining of the distal anal canal. If present for less than 6 weeks they are defined as acute, and chronic if present for more than 6 weeks.
Risk factors
- constipation
- inflammatory bowel disease
- sexually transmitted infections e.g. HIV, syphilis, herpes

Features
- painful, bright red, rectal bleeding
- around 90% of anal fissures occur on the posterior midline.
  - if the fissures are found in alternative locations then other underlying causes should be considered e.g. Crohn's disease

Management of an acute anal fissure (< 6 weeks)
- dietary advice: high-fibre diet with high fluid intake
- bulk-forming laxatives are first-line - if not tolerated then lactulose should be tried
- lubricants such as petroleum jelly may be tried before defecation

- topical anaesthetics
- analgesia
- topical steroids do not provide significant relief

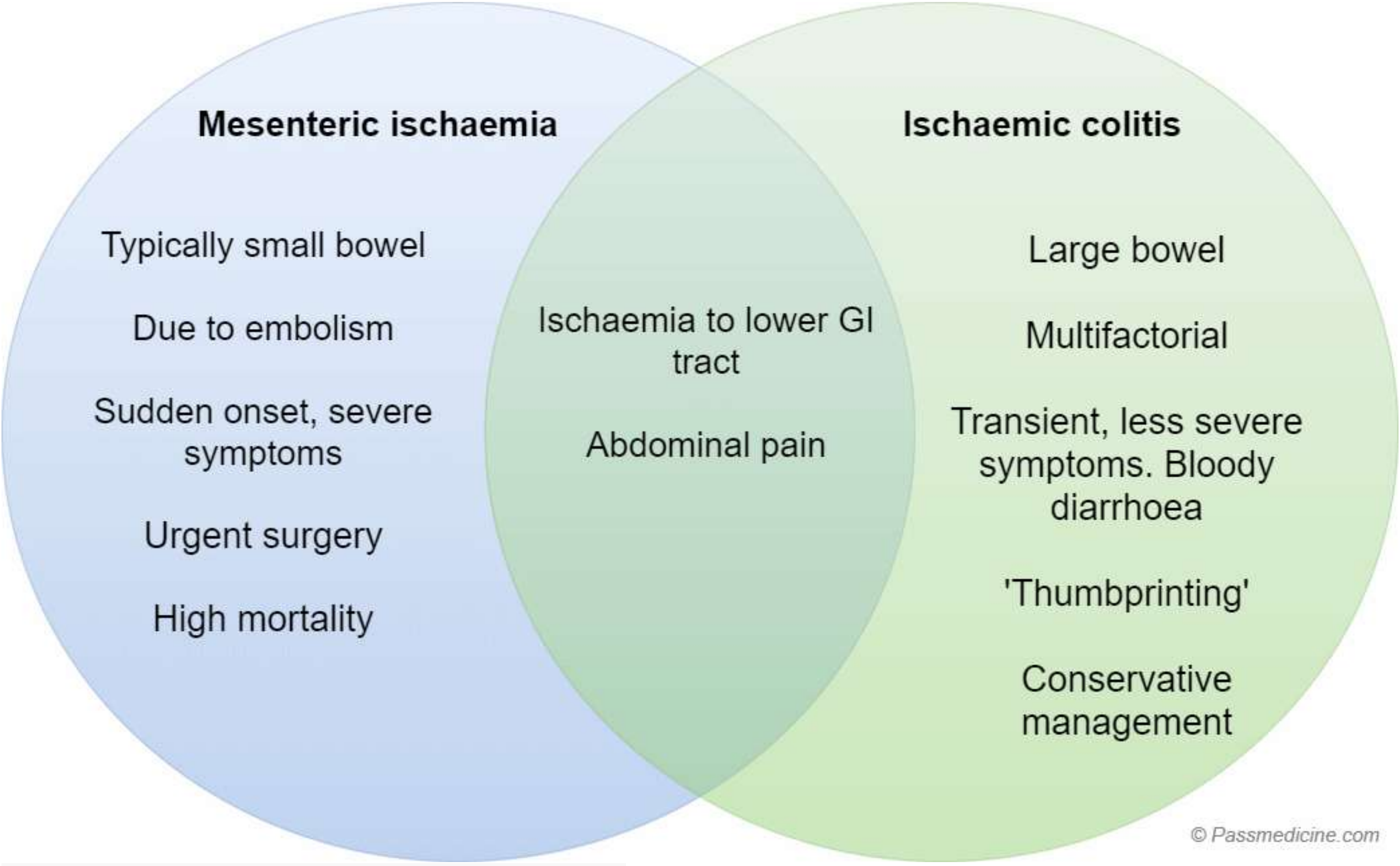
Management of a chronic anal fissure (> 6 weeks)

- the above techniques should be continued
- topical glyceryl trinitrate (GTN) is first-line treatment for a chronic anal fissure
- if topical GTN is not effective after 8 weeks then secondary care referral should be considered for surgery (sphincterotomy) or botulinum toxin

# ISCHAEMIA TO THE LOWER GASTROINTESTINAL TRACT

Ischaemia to the lower gastrointestinal tract can result in a variety of clinical conditions. Whilst there is no standard classification it can be useful to separate cases into 3 main conditions

- acute mesenteric ischaemia
- chronic mesenteric ischaemia
- ischaemic colitis


Mesenteric ischaemia
Typically small bowel
Due to embolism
Sudden onset, severe symptoms
Urgent surgery
High mortality
Ischaemia to lower GI tract
Abdominal pain
Ischaemic colitis
Large bowel
Multifactorial
Transient, less severe symptoms. Bloody diarrhoea
'Thumbprinting'
Conservative management
© Passmedicine.com

Venn diagram showing types of bowel ischaemia

**Common features in bowel ischaemia**

Common predisposing factors

- increasing age
- atrial fibrillation - particularly for mesenteric ischaemia
- other causes of emboli: endocarditis, malignancy
- cardiovascular disease risk factors: smoking, hypertension, diabetes
- cocaine: ischaemic colitis is sometimes seen in young patients following cocaine use

Common features

- abdominal pain - in acute mesenteric ischaemia this is often of sudden onset, severe and out-of-keeping with physical exam findings
- rectal bleeding
- diarrhoea
- fever
- bloods typically show an elevated white blood cell count associated with a lactic acidosis

Diagnosis

- CT is the investigation of choice

### Acute mesenteric ischaemia

Acute mesenteric ischaemia is typically caused by an embolism resulting in occlusion of an artery which supplies the small bowel, for example the superior mesenteric artery. Classically patients have a history of atrial fibrillation.

The abdominal pain is typically severe, of sudden onset and out-of-keeping with physical exam findings.

Management

- urgent surgery is usually required
- poor prognosis, especially if surgery delayed

### Chronic mesenteric ischaemia

Chronic mesenteric ischaemia is a relatively rare clinical diagnosis due to it's non-specific features and may be thought of as 'intestinal angina'. Colickly, intermittent abdominal pain occurs.

### Ischaemiac colitis

Ischaemic colitis describes an acute but transient compromise in the blood flow to the large bowel. This may lead to inflammation, ulceration and haemorrhage. It is more likely to occur in 'watershed' areas such as the splenic flexure that are located at the borders of the territory supplied by the superior and inferior mesenteric arteries.

Investigations

- 'thumbprinting' may be seen on abdominal x-ray due to mucosal oedema/haemorrhage

Management
- usually supportive
- surgery may be required in a minority of cases if conservative measures fail. Indications would include generalised peritonitis, perforation or ongoing haemorrhage

# ISCHAEMIC COLITIS

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Investigations
- 'thumbprinting' may be seen on abdominal x-ray due to mucosal oedema/haemorrhage

# GROIN HERNIAS: COMPARISION

| | Direct inguinal hernia | Indirect inguinal hernia | Femoral hernia |
|---|---|---|---|
| **Anatomy** | Protrudes through Hesselback triangle<br>Passes medial to the inferior epigastric artery | Protrudes through the inguinal ring<br>Passes lateral to the inferior epigastric artery | Protrudes below the inguinal ligament, lateral to the pubic tubercle |
| **Cause** | Defect or weakness in the transversalis fascia area of the Hesselbach triangle | Failure of the processus vaginalis to close | |
| **Risk of strangulation** | Low risk of strangulation | Low risk of strangulation | High risk of strangulation |
| **Age** | Seen in adults | May occur in infants | Seen in adults |
| **Gender** | Much more common in males | Much more common in males | More common in females |

# ALCOHOLIC LIVER DISEASE

The STOPAH study (see reference) compared the two common treatments for alcoholic hepatitis, pentoxyphylline and prednisolone. It showed that prednisolone improved survival at 28 days and that pentoxyphylline did not improve outcomes.

Reference:
Thursz et al. Prednisolone or Pentoxifylline for Alcoholic Hepatitis. NEJM. 2015.

## ALCOHOLIC KETOACIDOSIS

Alcoholic ketoacidosis is a non-diabetic euglycaemic form of ketoacidosis. It occurs in people who regularly drink large amounts of alcohol. Often alcoholics will not eat regularly and may vomit food that they do eat, leading to episodes of starvation. Once the person becomes malnourished, after an alcohol binge the body can start to break down body fat, producing ketones. Hence the patient develops a ketoacidosis.

It typically presents with a pattern of:
- Metabolic acidosis
- Elevated anion gap
- Elevated serum ketone levels
- Normal or low glucose concentration

The most appropriate treatment is an infusion of saline & thiamine. Thiamine is required to avoid Wernicke encephalopathy or Korsakoff psychosis.

## NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease (NAFLD) is now the most common cause of liver disease in the developed world. It is largely caused by obesity and describes a spectrum of disease ranging from:
- steatosis - fat in the liver
- steatohepatitis - fat with inflammation, non-alcoholic steatohepatitis (NASH), see below
- progressive disease may cause fibrosis and liver cirrhosis

NAFLD is thought to represent the hepatic manifestation of the metabolic syndrome and hence insulin resistance is thought to be the key mechanism leading to steatosis.

Non-alcoholic steatohepatitis (NASH) is a term used to describe liver changes similar to those seen in alcoholic hepatitis in the absence of a history of alcohol abuse. It is relatively common and thought to affect around 3-4% of the general population. The progression of disease in patients with NASH may be responsible for a proportion of patients previously labelled as cryptogenic cirrhosis.

Associated factors
- obesity
- type 2 diabetes mellitus
- hyperlipidaemia
- jejunoileal bypass

- sudden weight loss/starvation

Features
- usually asymptomatic
- hepatomegaly
- ALT is typically greater than AST
- increased echogenicity on ultrasound

NICE produced guidelines on the investigation and management of NAFLD in 2016. Key points:
- there is no evidence to support screening for NAFLD in adults, even in at risk groups (e.g. type 2 diabetes)
- the guidelines are therefore based on the management of the incidental finding of NAFLD - typically asymptomatic fatty changes on liver ultrasound
- in these patients, NICE recommends the use of the enhanced liver fibrosis (ELF) blood test to check for advanced fibrosis
- the ELF blood test is a combination of hyaluronic acid + procollagen III + tissue inhibitor of metalloproteinase 1. An algorithm based on these values results in an ELF blood test score, similar to triple testing for Down's syndrome

An excellent review by Byrne et Al1 in 2018 reviewed the diagnosis and monitoring of NAFLD. It made the following suggestions if the ELF blood test was not available:
- non-invasive tests may be used to assess the severity of fibrosis
- these include the FIB4 score or NALFD fibrosis score
- these scores may be used in combination with a FibroScan (liver stiffness measurement assessed with transient elastography)
- this combination has been shown to have excellent accuracy in predicting fibrosis

Patients who are likely to have advanced fibrosis should be referred to a liver specialist. They will then likely have a liver biopsy to stage the disease more accurately.

Management
- the mainstay of treatment is lifestyle changes (particularly weight loss) and monitoring
- there is ongoing research into the role of gastric banding and insulin-sensitising drugs (e.g. metformin, pioglitazone)

**References**

1. BMJ 2018;362:k2734

# ANGIODYSPLASIA

Angiodysplasia is a vascular deformity of the gastrointestinal tract which predisposes to bleeding and iron deficiency anaemia. There is thought to be an association with aortic stenosis, although this is debated. Angiodysplasia is generally seen in elderly patients

Diagnosis
- colonoscopy
- mesenteric angiography if acutely bleeding

Management
- endoscopic cautery or argon plasma coagulation
- antifibrinolytics e.g. Tranexamic acid
- oestrogens may also be used

# CARCINOID TUMOURS

Carcinoid syndrome
- usually occurs when metastases are present in the liver and release serotonin into the systemic circulation
- may also occur with lung carcinoid as mediators are not 'cleared' by the liver

Features
- flushing (often earliest symptom)
- diarrhoea
- bronchospasm
- hypotension
- right heart valvular stenosis (left heart can be affected in bronchial carcinoid)
- other molecules such as ACTH and GHRH may also be secreted resulting in, for example, Cushing's syndrome
- pellagra can rarely develop as dietary tryptophan is diverted to serotonin by the tumour

Investigation
- urinary 5-HIAA
- plasma chromogranin A y

Management
- somatostatin analogues e.g. octreotide
- diarrhoea: cyproheptadine may help

# CHOLANGIOCARCINOMA

Features
- persistent biliary colic symptoms
- associated with anorexia, jaundice and weight loss
- a palpable mass in the right upper quadrant (Courvoisier sign),
- periumbilical lymphadenopathy (Sister Mary Joseph nodes) and left supraclavicular adenopathy (Virchow node) may be seen

# COMPLICATIONS FOLLOWING RENAL TRANSPLANT

Renal transplantation is widely practised. The commonest technical related complications are related to the ureteric anastomosis. The warm ischaemic time is also of considerable importance and graft survival is directly related to this. Long warm ischaemic times increase the risk of acute tubular necrosis which may occur in all types of renal transplanation and provided other insults are minimised, will usually recover. Organ rejection may occur at any phase following the transplantation process.

**Immunological complications**
**Types of organ rejection**

- Hyperacute. This occurs immediately through presence of pre formed antibody (such as ABO incompatibility).
- Acute. Occurs during the first 6 months and is usually T cell mediated. Usually tissue infiltrates and vascular lesions.
- Chronic. Occurs after the first 6 months. Vascular changes predominate.

**Hyperacute**
Renal transplants are most susceptible to this process. Risk factors include major HLA mismatch and ABO incompatibility. The rejection occurs almost immediately and the macroscopic features may become manifest following completion of the vascular anastomosis and removal of clamps. The kidney becomes mottled, dusky and the vessels will thrombose. The only treatment is removal of the graft, if left in situ it will result in abscess formation.

**Acute**
All organs may undergo acute rejection. Mononuclear cell infiltrates predominate. All types of transplanted organ are susceptible and it may occur in up to 50% cases. Most cases can be managed medically.

**Chronic**
Again all transplants with HLA mismatch may suffer this fate. Previous acute rejections and other immunosensitising events all increase the risk. Vascular changes are most prominent with myointimal proliferation leading to organ ischaemia. Organ specific changes are also seen such as

loss of acinar cells in pancreas transplants and rapidly progressive coronary artery disease in cardiac transplants.

**Technical complications**

| Complication | Presenting features | Treatment |
|---|---|---|
| Renal artery thrombosis | Sudden complete loss of urine output | Immediate surgery may salvage the graft, delays beyond 30 minutes are associated with a high rate of graft loss |
| Renal artery stenosis | Uncontrolled hypertension, allograft dysfunction and oedema | Angioplasty is the treatment of choice |
| Renal vein thrombosis | Pain and swelling over the graft site, haematuria and oliguria | The graft is usually lost |
| Urine leaks | Diminished urine output, rising creatinine, fever and abdominal pain | USS shows perigraft collection, necrosis of ureter tip is the commonest cause and the anastomosis may need revision |
| Lymphocele | Common complication (occurs in 15%), may present as a mass, if large may compress ureter | May be drained with percutaneous technique and sclerotherapy, or intraperitoneal drainage |

# TRAUMA MANAGEMENT

The cornerstone of trauma management is embodied in the principles of ATLS.

Following trauma there is a trimodal death distribution:

- **Immediately** following injury. Typically as result of brain or high spinal injuries, cardiac or great vessel damage. Salvage rate is low.
- In **early hours** following injury. In this group deaths are due to phenomena such as splenic rupture, subdural haematomas and haemopneumothoraces
- In the **days** following injury. Usually due to sepsis or multi organ failure.

**Aspects of trauma management**

- ABCDE approach.
- Tension pneumothoraces will deteriorate with vigorous ventilation attempts.
- External haemorrhage is managed as part of the primary survey. As a rule tourniquets should not be used. Blind application of clamps will tend to damage surrounding structures and packing is the preferred method of haemorrhage control.
- Urinary catheters and naso gastric tubes may need inserting. Be wary of basal skull fractures and urethral injuries.
- Patients with head and neck trauma should be assumed to have a cervical spine injury until proven otherwise.

**Thoracic injuries**

- Simple pneumothorax
- Mediastinal traversing wounds
- Tracheobronchial tree injury
- Haemothorax
- Blunt cardiac injury
- Diaphragmatic injury
- Aortic disruption
- Pulmonary contusion

**Management of thoracic trauma**

- **Simple pneumothorax** insert chest drain. Aspiration is risky in trauma as pneumothorax may be from lung laceration and convert to tension pneumothorax.
- **Mediastinal traversing wounds** These result from situations like stabbings. Exit and entry wounds in separate hemithoraces. The presence of a mediastinal haematoma indicates the likelihood of a great vessel injury. All patients should undergo CT angiogram and oesophageal contrast swallow. Indications for thoracotomy are largely related to blood loss and will be addressed below.
- **Tracheobronchial tree injury** Unusual injuries. In blunt trauma most injuries occur within 4cm of the carina. Features suggesting this injury include haemoptysis and surgical emphysema. These injuries have a very large air leak and may have tension pneumothorax.
- **Haemothorax** Usually caused by laceration of lung vessel or internal mammary artery by rib fracture. Patients should all have a wide bore 36F chest drain. Indications for thoracotomy include loss of more than 1.5L blood initially or ongoing losses of >200ml per hour for >2 hours.
- **Cardiac contusions** Usually cardiac arrhythmias, often overlying sternal fracture. Perform echocardiography to exclude pericardial effusions and tamponade. Risk of arrhythmias falls after 24 hours.
- **Diaphragmatic injury** Usually left sided. Direct surgical repair is performed.
- **Traumatic aortic disruption** Commonest cause of death after RTA or falls. Usually incomplete laceration near ligamentum arteriosum. All survivors will have contained haematoma. Only 1-2% of patients with this injury will have a normal chest x-ray.
- **Pulmonary contusion** Common and lethal. Insidious onset. Early intubation and ventilation.

**Abdominal trauma**

- Deceleration injuries are common.
- In blunt trauma requiring laparotomy the spleen is most commonly injured (40%)
- Stab wounds traverse structures most commonly liver (40%)
- Gunshot wounds have variable effects depending upon bullet type. Small bowel is most commonly injured (50%)
- Patients with stab wounds and no peritoneal signs up to 25% will not enter the peritoneal cavity
- Blood at urethral meatus suggests a urethral tear
- High riding prostate on PR = urethral disruption
- Mechanical testing for pelvic stability should only be performed once

### Investigations in abdominal trauma

| | Diagnostic Peritoneal Lavage | Abdominal CT scan | USS |
|---|---|---|---|
| **Indication** | Document bleeding if hypotensive | Document organ injury if normotensive | Document fluid if hypotensive |
| **Advantages** | Early diagnosis and sensitive; 98% accurate | Most specific for localising injury; 92 to 98% accurate | Early diagnosis, non invasive and repeatable; 86 to 95% accurate |
| **Disadvantages** | Invasive and may miss retroperitoneal and diaphragmatic injury | Location of scanner away from facilities, time taken for reporting, need for contrast | Operator dependent and may miss retroperitoneal injury |

# PASSMEDICINE NOTES INFECTIOUS DISEASES

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# CLASSIFICATION OF BACTERIA

Remember:
- Gram-positive cocci = staphylococci + streptococci (including enterococci)
- Gram-negative cocci = Neisseria meningitidis + Neisseria gonorrhoeae, also Moraxella catarrhalis

Therefore, only a small list of Gram-positive rods (bacilli) need to be memorised to categorise all bacteria - mnemonic = ABCD L
- *Actinomyces*
- *Bacillus anthracis* (anthrax)
- *Clostridium*
- Diphtheria*: Corynebacterium diphtheriae*
- *Listeria monocytogenes*

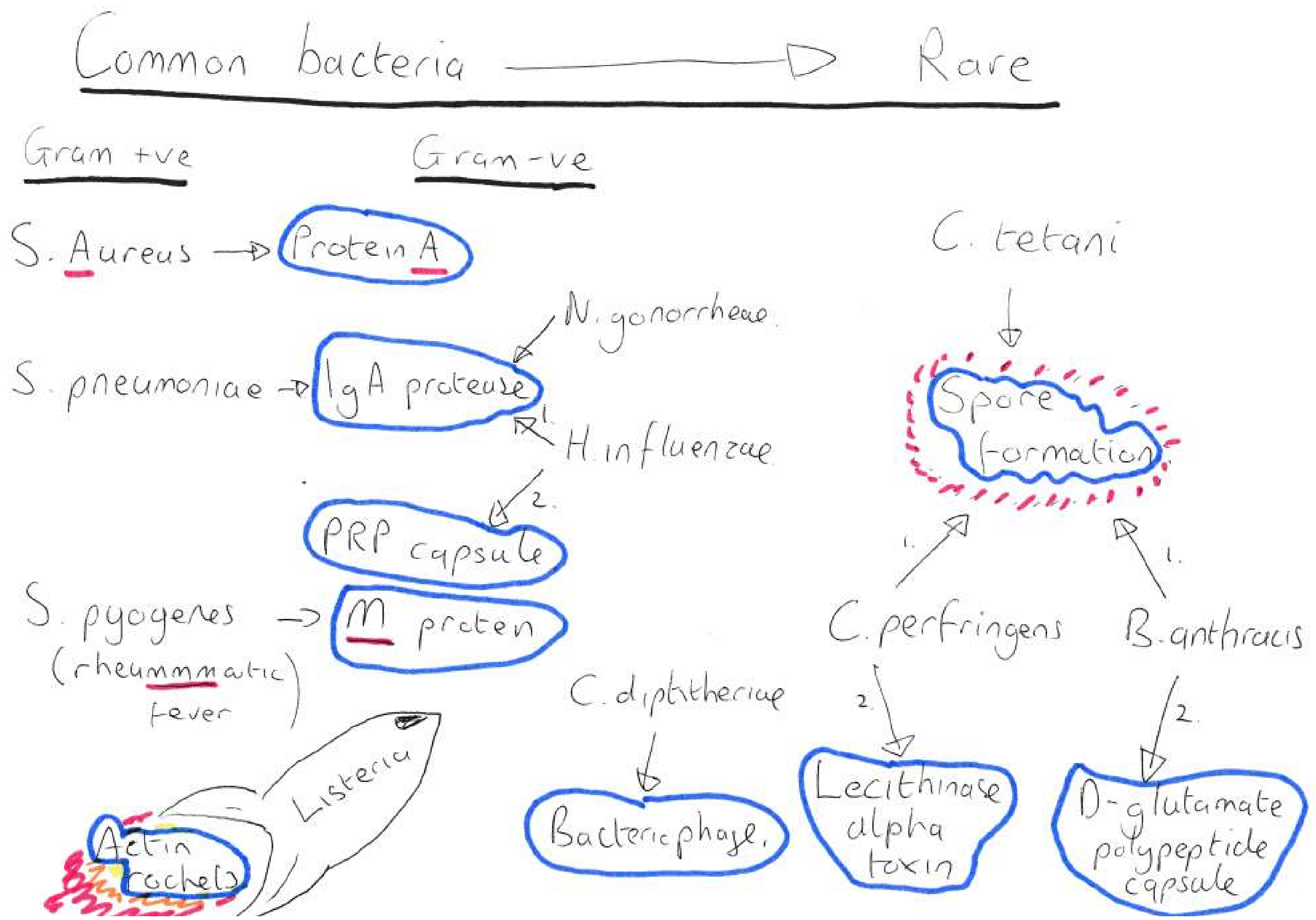
Remaining organisms are Gram-negative rods, e.g.:
- *Escherichia coli*
- *Haemophilus influenzae*
- *Pseudomonas aeruginosa*
- *Salmonella sp.*
- *Shigella sp.*
- *Campylobacter jejuni*

# VIRULENCE FACTORS

Bacteria employ a large number of virulence factors which enable them to colonize the host and evade/suppress the immune response. The table below shows a select number of virulence factors which are important for the exam.

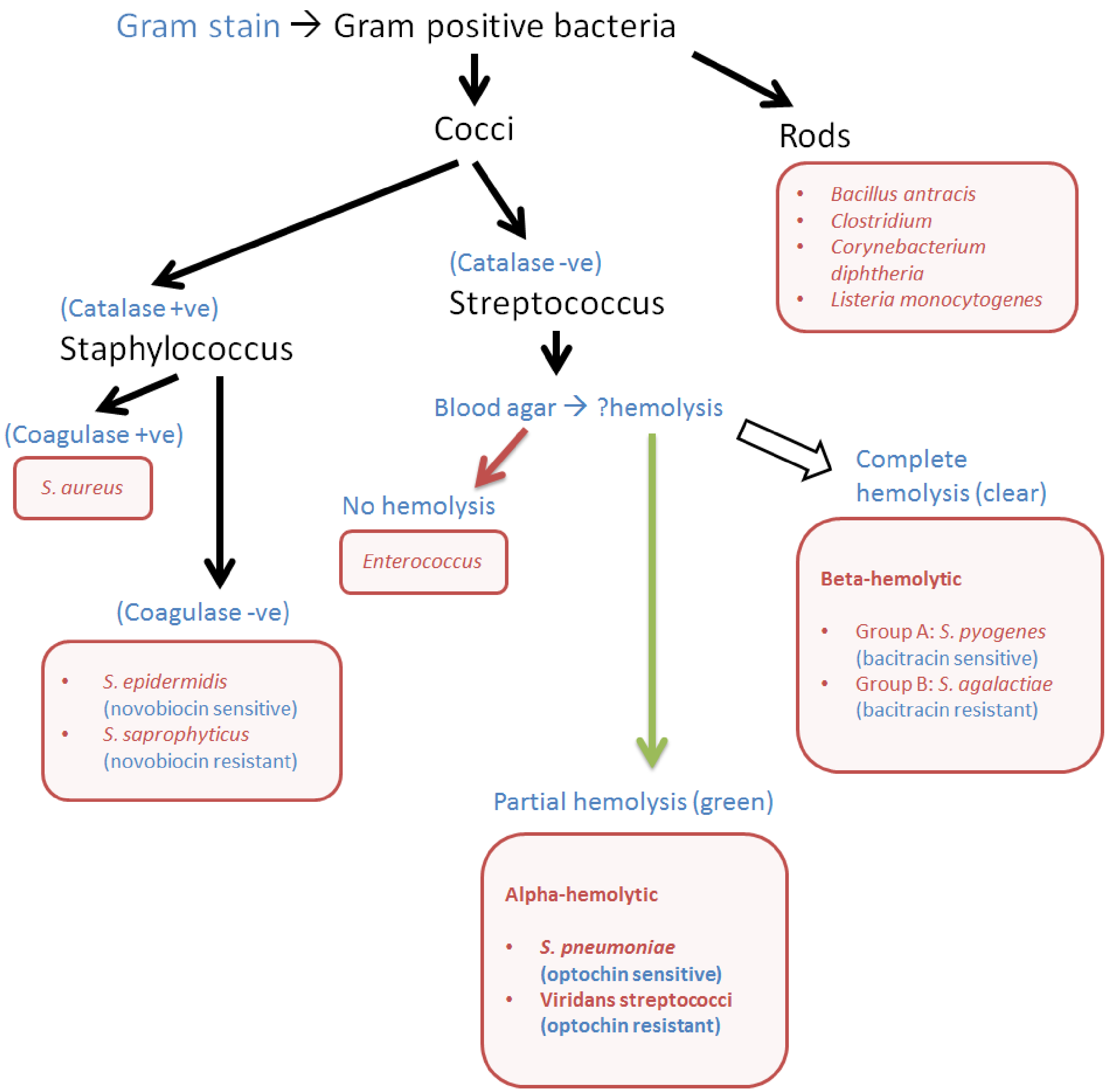
| Virulence factor | Example organisms |
|---|---|
| IgA protease | *Streptococcus pneumoniae*<br>*Haemophilus influenzae*<br>*Neisseria gonorrhoeae* |
| M Protein | *Streptococcus pyogenes* |
| Polyribosyl ribitol phosphate capsule | *Haemophilus influenzae* |
| Bacteriophage | *Corynebacterium diphtheriae* |
| Spore formation | *Bacillus anthracis*<br>*Clostridium perfringens*<br>*Clostridium tetani* |
| Lecithinase alpha toxin | *Clostridium perfringens* |
| D-glutamate polypeptide capsule | *Bacillus anthracis* |

| Virulence factor | Example organisms |
|---|---|
| Actin rockets | *Listeria monocytogenes* |


Common bacteria → Rare
Gram +ve
Gram -ve
S. Aureus
Protein A
N. gonorrheae
S. pneumoniae
IgA protease
1.
H. influenzae
2.
PRP capsule
S. pyogenes
(rheummmatic fever)
M protein
Listeria
Actin rockets
C. diphtheriae
Bacteriophage.
C. tetani
Spore formation
1.
1.
C. perfringens
B. anthracis
2.
2.
Lecithinase alpha toxin
D-glutamate polypeptide capsule

# IDENTIFYING GRAM-POSITIVE BACTERIA

Gram-positive bacteria will turn purple/blue following the gram staining. Microscopy will then reveal the shape, either cocci or rods.


Gram stain → Gram positive bacteria
Cocci
Rods
Bacillus antracis
Clostridium
Corynebacterium diphtheria
Listeria monocytogenes
(Catalase +ve)
Staphylococcus
(Catalase -ve)
Streptococcus
(Coagulase +ve)
S. aureus
(Coagulase -ve)
S. epidermidis (novobiocin sensitive)
S. saprophyticus (novobiocin resistant)
Blood agar → ?hemolysis
No hemolysis
Enterococcus
Complete hemolysis (clear)
Beta-hemolytic
Group A: S. pyogenes (bacitracin sensitive)
Group B: S. agalactiae (bacitracin resistant)
Partial hemolysis (green)
Alpha-hemolytic
S. pneumoniae (optochin sensitive)
Viridans streptococci (optochin resistant)

Rods (bacilli)

- *Actinomyces*
- *Bacillus antracis*
- *Clostridium*
- *Corynebacterium diphtheriae*
- *Listeria monocytogenes*

Cocci

- makes catalase: Staphylococci
- does not make catalase: Streptococci

Staphylococci
- makes coagulase: S. aureus
- does not make coagulase: S. epidermidis (novobiocin sensitive), S. saprophyticus (novobiocin resistant)

Streptococci
- partial haemolysis (green colour on blood agar): α-haemolytic
- complete haemolysis (clear): β-haemolytic
- no haemolysis: γ-haemolytic

α-haemolytic streptococci
- optochin sensitive: S. pneumoniae
- optochin resistant: Viridans streptococci

β-haemolytic streptococci
- bacitracin sensitive: Group A: S. pyogenes
- bacitracin resistant: Group B: S. agalactiae

# STREPTOCOCCI

Streptococci are gram-positive cocci. They may be divided into alpha and beta haemolytic types

**Alpha haemolytic streptococci (partial haemolysis)**
The most important alpha haemolytic Streptococcus is Streptococcus pneumoniae (pneumococcus). Pneumococcus is a common cause of pneumonia, meningitis and otitis media. Another clinical example is Streptococcus viridans

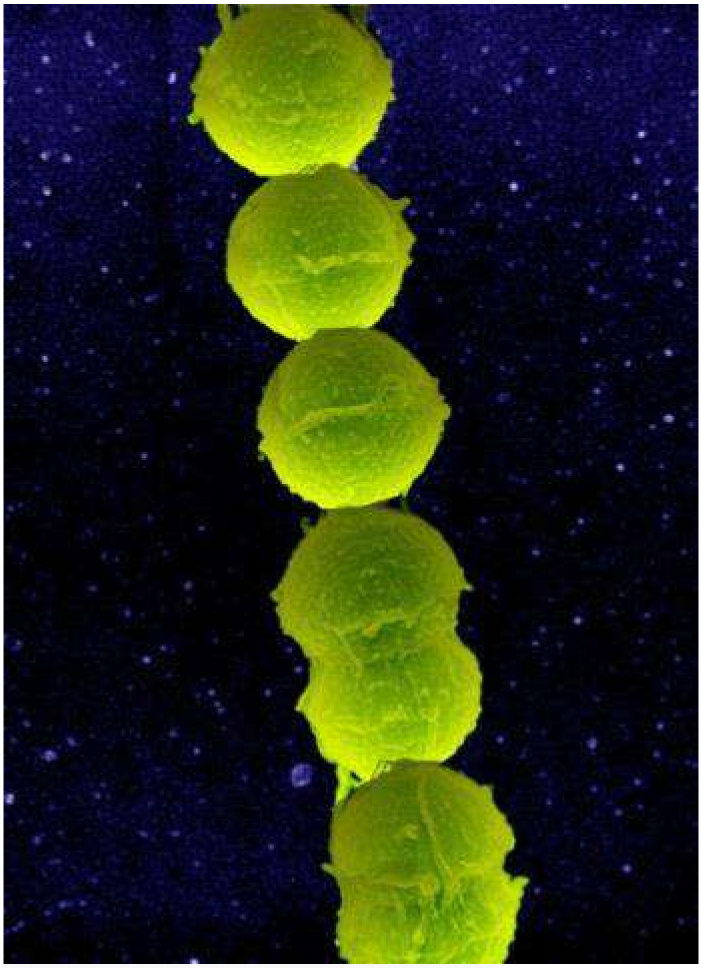
**Beta haemolytic streptococci (complete haemolysis)**
These can be subdivided into groups A-H. Only groups A, B & D are important in humans.

Group A
- most important organism is Streptococcus pyogenes
- responsible for erysipelas, impetigo, cellulitis, type 2 necrotizing fasciitis and pharyngitis/tonsillitis
- immunological reactions can cause rheumatic fever or post-streptococcal glomerulonephritis
- erythrogenic toxins cause scarlet fever

Group B
- Streptococcus agalactiae may lead to neonatal meningitis and septicaemia

Group D

- Enterococcus



Group B streptococcus bacteria. Credit: NIAID

## CLOSTRIDIA

Clostridia are gram-positive, obligate anaerobic bacilli.

*C. perfringens*

- produces α-toxin, a lecithinase, which causes gas gangrene (myonecrosis) and haemolysis
- features include tender, oedematous skin with haemorrhagic blebs and bullae. Crepitus may present on palpation

*C. botulinum*

- typically seen in canned foods and honey
- prevents acetylcholine (ACh) release leading to flaccid paralysis

*C. difficile*

- causes pseudomembranous colitis, typically seen after the use of broad-spectrum antibiotics

- produces both an exotoxin and a cytotoxin

*C. tetani*
- produces an exotoxin (tetanospasmin) that prevents the release of glycine from Renshaw cells in the spinal cord causing a spastic paralysis

# ENTERIC FEVER (TYPHOID/PARATYPHOID)

The Salmonella group contains many members, most of which cause diarrhoeal diseases. They are aerobic, Gram-negative rods which are not normally present as commensals in the gut.

Typhoid and paratyphoid are caused by Salmonella typhi and Salmonella paratyphi (types A, B & C) respectively. They are often termed enteric fevers, producing systemic symptoms such as headache, fever, arthralgia.

Pathophysiology
typhoid is transmitted via the faecal-oral route (also in contaminated food and water)

Features
- initially systemic upset as above
- relative bradycardia
- abdominal pain, distension
- constipation: although Salmonella is a recognised cause of diarrhoea, constipation is more common in typhoid
- rose spots: present on the trunk in 40% of patients, and are more common in paratyphoid

Possible complications include
- osteomyelitis (especially in sickle cell disease where Salmonella is one of the most common pathogens)
- GI bleed/perforation
- meningitis
- cholecystitis
- chronic carriage (1%, more likely if adult females)

# ANIMAL AND HUMAN BITES

**Animal bites**
The majority of bites seen in everyday practice involve dogs and cats. These are generally polymicrobial but the most common isolated organism is Pasteurella multocida.

Management
- cleanse wound. Puncture wounds should not be sutured closed unless cosmesis is at risk
- current BNF recommendation is co-amoxiclav
- if penicillin-allergic then doxycycline + metronidazole is recommended

**Human bites**
Human bites commonly cause multimicrobial infection, including both aerobic and anaerobic bacteria.

Common organisms include:
- *Streptococci spp.*
- *Staphylococcus aureus*
- *Eikenella*
- *Fusobacterium*
- *Prevotella*

Co-amoxiclav is recommended, as for animal bites.

The risk of viral infections such as HIV and hepatitis C should also be considered.

# CAT SCRATCH DISEASE

Cat scratch disease is generally caused by the Gram negative rod Bartonella henselae

Features
- fever
- history of a cat scratch
- regional lymphadenopathy
- headache, malaise

# ANTHRAX

Anthrax is caused by Bacillus anthracis, a Gram positive rod. It is spread by infected carcasses. It is also known as Woolsorters' disease. Bacillus anthracis produces a tripartite protein toxin
- protective antigen
- oedema factor: a bacterial adenylate cyclase which increases cAMP
- lethal factor: toxic to macrophages

Features
- causes painless black eschar (cutaneous 'malignant pustule', but no pus)
- typically painless and non-tender

- may cause marked oedema
- anthrax can cause gastrointestinal bleeding

Management
- the current Health Protection Agency advice for the initial management of cutaneous anthrax is ciprofloxacin
- further treatment is based on microbiological investigations and expert advice

## CRYPTOSPORIDIOSIS

Cryptosporidiosis is the commonest protozoal cause of diarrhoea in the UK. Two species, Cryptosporidium hominis and Cryptosporidium parvum account for the majority cases.

Cryptosporidiosis is more common in immunocompromised patients (e.g. HIV) and young children.

Features
- watery diarrhoea
- abdominal cramps
- fever
- in immunocompromised patients the entire gastrointestinal tract may be affected resulting in complications such as sclerosing cholangitis and pancreatitis

Diagnosis
- stool: modified Ziehl-Neelsen stain (acid-fast stain) of the stool may reveal the characteristic red cysts of Cryptosporidium

Management
- is largely supportive
- nitazoxanide is licensed in the US for immunocompetent patients

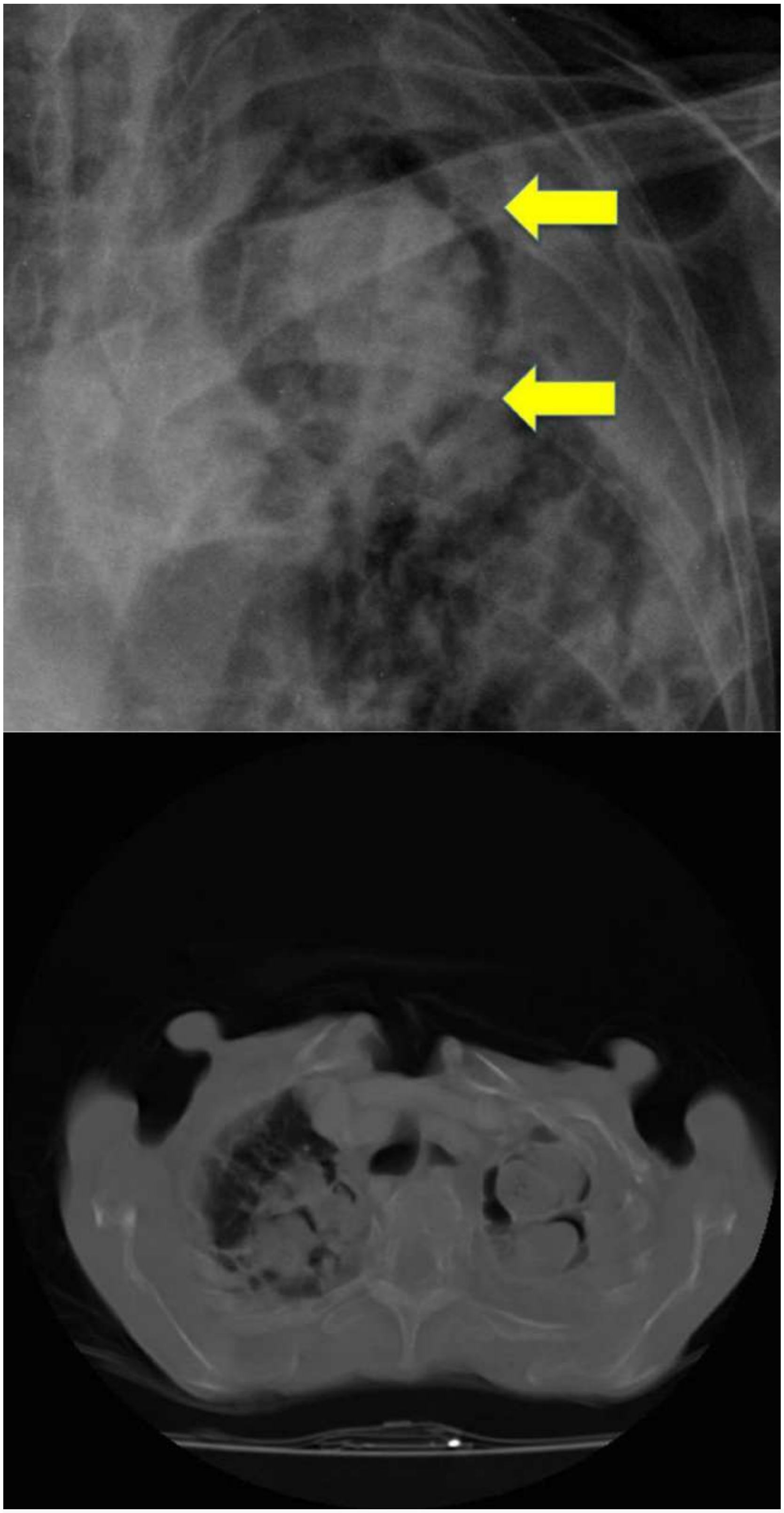
## ASPERGILLOMA

An aspergilloma is a mycetoma (mass-like fungus ball) which often colonises an existing lung cavity (e.g. secondary to tuberculosis, lung cancer or cystic fibrosis).

Usually asymptomatic but features may include
- cough
- haemoptysis (may be severe)

Investigations

- chest x-ray containing a rounded opacity. A crescent sign may be present
- high titres Aspergillus precipitins



Aspergilloma in a patient with cavities secondary to previous tuberculosis infection. The close-up CXR and CT scan from the same patient demonstrate a rounded soft tissue attenuating masses located in a surrounding cavity.

# STI: ULCERS

Genital herpes is most often caused by the herpes simplex virus (HSV) type 2 (cold sores are usually due to HSV type 1). Primary attacks are often severe and associated with fever whilst subsequent attacks are generally less severe and localised to one site. There is typically multiple painful ulcers.

Syphilis is a sexually transmitted infection caused by the spirochaete Treponema pallidum. Infection is characterised by primary, secondary and tertiary stages. A painless ulcer (chancre) is seen in the primary stage. The incubation period= 9-90 days.

Chancroid is a tropical disease caused by Haemophilus ducreyi. It causes painful genital ulcers associated with unilateral, painful inguinal lymph node enlargement. The ulcers typically have a sharply defined, ragged, undermined border.

Lymphogranuloma venereum (LGV) is caused by Chlamydia trachomatis. Typically infection comprises of three stages
stage 1: small painless pustule which later forms an ulcer
stage 2: painful inguinal lymphadenopathy
stage 3: proctocolitis

LGV is treated using doxycycline.

Other causes of genital ulcers

- Behcet's disease
- carcinoma
- granuloma inguinale: *Klebsiella granulomatis**

*previously called *Calymmatobacterium granulomatis*

# SYPHILIS

Syphilis is a sexually transmitted infection caused by the spirochaete Treponema pallidum. Infection is characterised by primary, secondary and tertiary stages. The incubation period is between 9-90 days

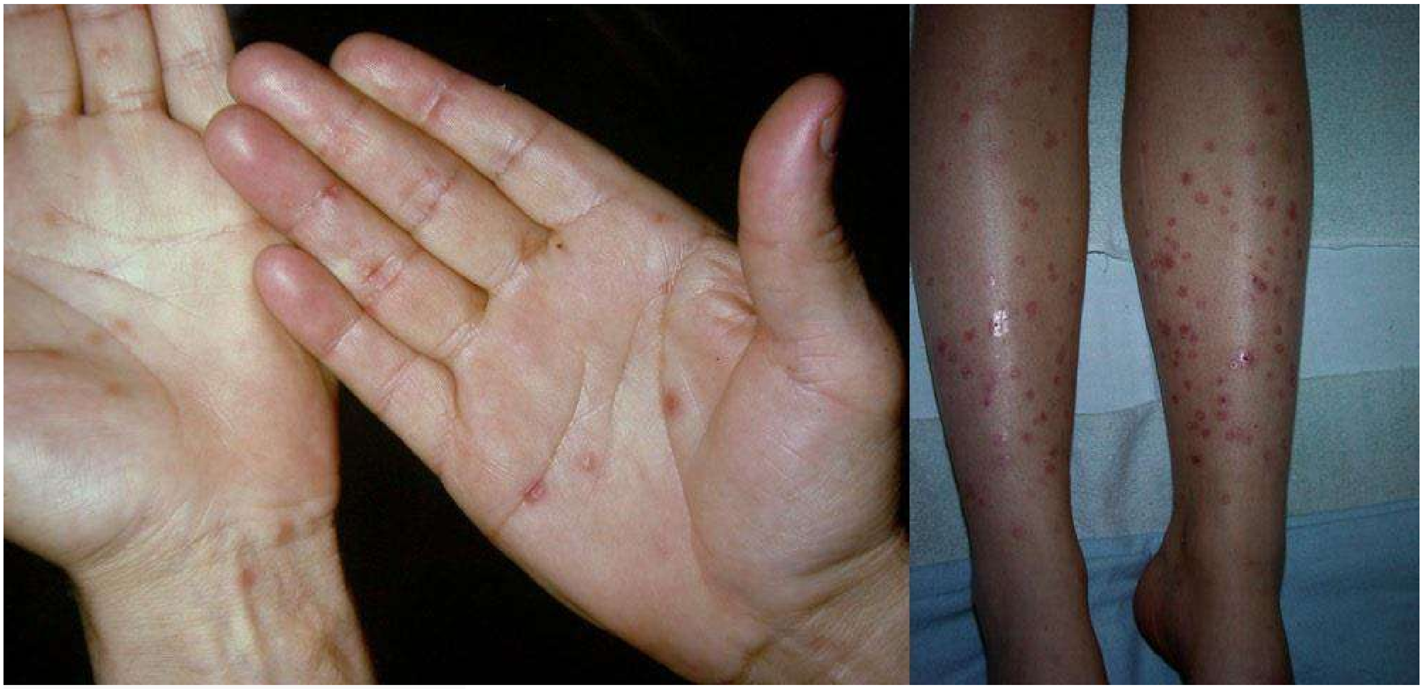
Primary features

- chancre - painless ulcer at the site of sexual contact
- local non-tender lymphadenopathy
- often not seen in women (the lesion may be on the cervix)

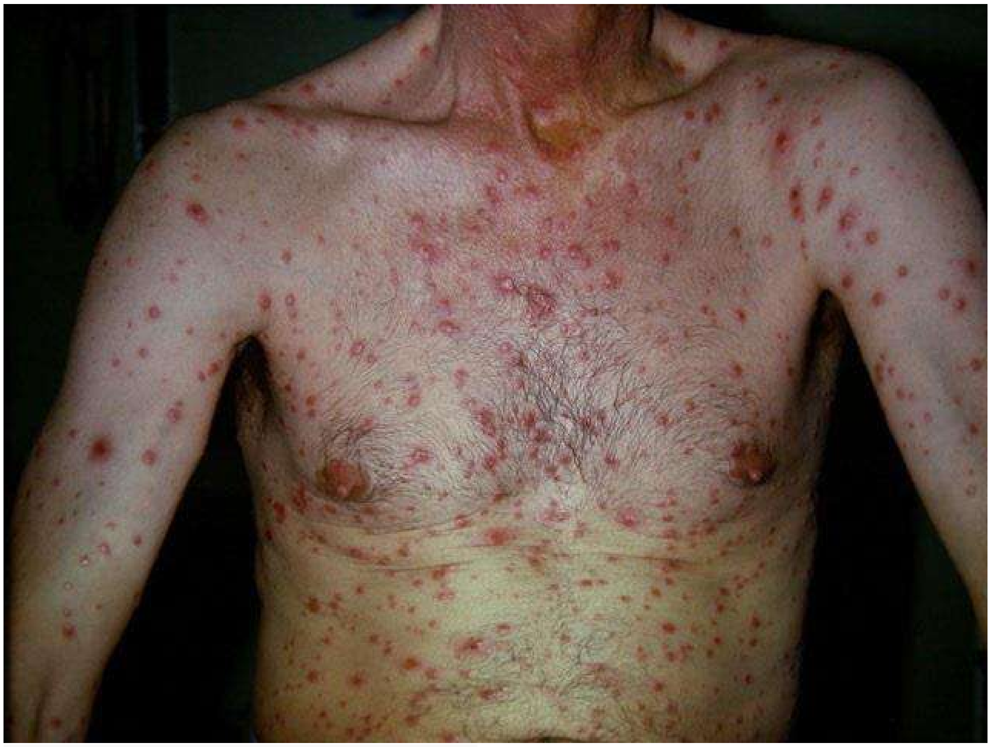
Secondary features - occurs 6-10 weeks after primary infection

- systemic symptoms: fevers, lymphadenopathy

- rash on trunk, palms and soles
- buccal 'snail track' ulcers (30%)
- condylomata lata (painless, warty lesions on the genitalia )



Classical palm lesions of secondary syphilis



More generalised rash of secondary syphilis

Tertiary features

- gummas (granulomatous lesions of the skin and bones)
- ascending aortic aneurysms

- general paralysis of the insane
- tabes dorsalis
- Argyll-Robertson pupil

Features of congenital syphilis
- blunted upper incisor teeth (Hutchinson's teeth), 'mulberry' molars
- rhagades (linear scars at the angle of the mouth)
- keratitis
- saber shins
- saddle nose
- deafness

## SYPHILIS: INVESTIGATION

*Treponema pallidum* is a very sensitive organism and cannot be grown on artificial media. The diagnosis is therefore usually based on clinical features, serology and microscopic examination of infected tissue

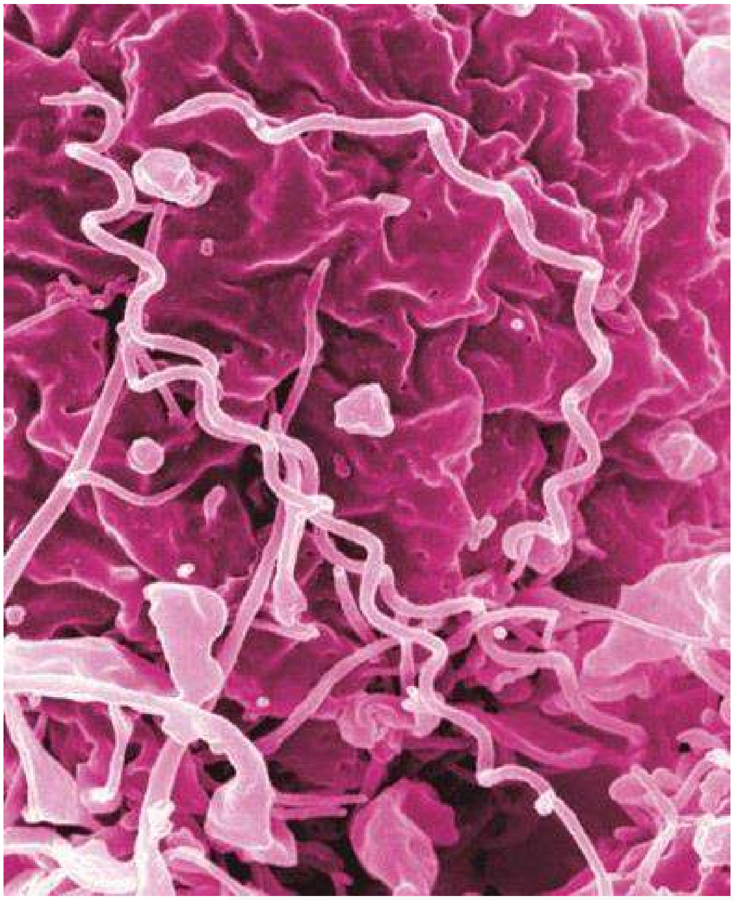
Serological tests can be divided into:
- cardiolipin tests (not treponeme specific)
- treponemal-specific antibody tests

Cardiolipin tests
- syphilis infection leads to the production of non-specific antibodies that react to cardiolipin
- examples include VDRL (Venereal Disease Research Laboratory) & RPR (rapid plasma reagin)
- insensitive in late syphilis
- becomes negative after treatment

Treponemal specific antibody tests
- example: TPHA (Treponema pallidum HaemAgglutination test)
- remains positive after treatment

Therefore, following treatment for syphilis:
- VDRL becomes negative
- TPHA remains positive

Causes of false positive cardiolipin tests:
- pregnancy
- SLE, anti-phospholipid syndrome
- TB
- leprosy
- malaria
- HIV



*Treponema pallidum*, the bacteria that cause syphilis. Note the spiral shape of the organism. Credit: NIAID

## SYPHILIS: MANAGEMENT

Management

- intramuscular benzathine penicillin is the first-line management
- alternatives: doxycycline
- the Jarisch-Herxheimer reaction is sometimes seen following treatment
  - fever, rash, tachycardia after the first dose of antibiotic
  - in contrast to anaphylaxis, there is no wheeze or hypotension
  - it is thought to be due to the release of endotoxins following bacterial death and typically occurs within a few hours of treatment
  - No treatment is needed other than antipyretics if required

## CHANCROID

Chancroid is a tropical disease caused by Haemophilus ducreyi. It causes painful genital ulcers associated with unilateral, painful inguinal lymph node enlargement. The ulcers typically have a sharply defined, ragged, undermined border.

# GENITAL HERPES

There are two strains of the herpes simplex virus (HSV) in humans: HSV-1 and HSV-2. Whilst it was previously thought HSV-1 accounted for oral lesions (cold sores) and HSV-2 for genital herpes it is now known there is considerable overlap

Features
- primary infection: may present with a severe ulceration and pain
- urinary retention may occur
- painful genital ulceration

Management
- genital herpes: oral aciclovir. Some patients with frequent exacerbations may benefit from longer term aciclovir

Pregnancy
- elective caesarean section at term is advised if a primary attack of herpes occurs during pregnancy at greater than 28 weeks gestation
- women with recurrent herpes who are pregnant should be treated with suppressive therapy and be advised that the risk of transmission to their baby is low

# GENITAL WARTS

Genital warts (also known as condylomata accuminata) are a common cause of attendance at genitourinary clinics. They are caused by the many varieties of the human papilloma virus HPV, especially types 6 & 11. It is now well established that HPV (primarily types 16,18 & 33) predisposes to cervical cancer.

Features
- small (2 - 5 mm) fleshy protuberances which are slightly pigmented
- may bleed or itch

Management
- topical podophyllum or cryotherapy are commonly used as first-line treatments depending on the location and type of lesion. Multiple, non-keratinised warts are generally best treated with topical agents whereas solitary, keratinised warts respond better to cryotherapy
- imiquimod is a topical cream which is generally used second line
- genital warts are often resistant to treatment and recurrence is common although the majority of anogenital infections with HPV clear without intervention within 1-2 years

# HUMAN PAPILLOMA VIRUS VACCINATION

It has been known for a longtime that the human papilloma virus (HPV) which infects the keratinocytes of the skin and mucous membranes is carcinogenic.

There are dozens of strains of HPV. The most important to remember are:
- 6 & 11: causes genital warts
- 16 & 18: linked to a variety of cancers, most notably cervical cancer

HPV infection is linked to:
- over 99.7% of cervical cancers
- around 85% of anal cancers
- around 50% of vulval and vaginal cancers
- around 20-30% of mouth and throat cancers

It should of course be remembered that there are other risk factors important in developing cervical cancer such as smoking, combined oral contraceptive pill use and high parity.

Testing for HPV has now been integrated into the cervical cancer screening programme. If a smear is reported as borderline or mild dyskaryosis the original sample is tested for HPV
- if HPV negative the patient goes back to routine recall
- if HPV positive the patient is referred for colposcopy

**Immunisation**
A vaccination for HPV was introduced in the UK back in 2008. As you may remember the Department of Health initially chose Cervarix. This vaccine protected against HPV 16 & 18 but not 6 & 11. There was widespread criticism of this decision given the significant disease burden caused by genital warts. Eventually in 2012 Gardasil replaced Cervarix as the vaccine used. Gardasil protects against HPV 6, 11, 16 & 18. This was initially just given to girls but from September 2019 boys were given the vaccine as well.

From September 2019, **all 12- and 13-year-olds (girls AND boys)** in school Year 8 will be offered the human papillomavirus (HPV) vaccine.
- the vaccine is normally given in school
- information given to parents and available on the NHS website make it clear that the daughter may receive the vaccine against parental wishes
- given as 2 doses - girls have the second dose between 6-24 months after the first, depending on local policy

HPV vaccination should also be offered to men who have sex with men under the age of 45 to protect against anal, throat and penile cancers.

Injection site reactions are particularly common with HPV vaccines.

# CHLAMYDIA

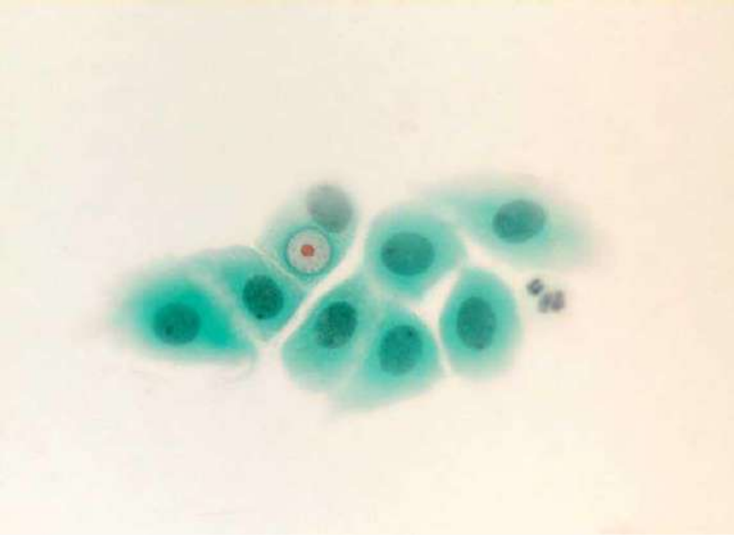
*Chlamydia* is the most prevalent sexually transmitted infection in the UK and is caused by Chlamydia trachomatis, an obligate intracellular pathogen. Approximately 1 in 10 young women in the UK have Chlamydia. The incubation period is around 7-21 days, although it should be remembered a large percentage of cases are asymptomatic

Features
- asymptomatic in around 70% of women and 50% of men
- women: cervicitis (discharge, bleeding), dysuria
- men: urethral discharge, dysuria

Potential complications
- epididymitis
- pelvic inflammatory disease
- endometritis
- increased incidence of ectopic pregnancies
- infertility
- reactive arthritis
- perihepatitis (Fitz-Hugh-Curtis syndrome)

Investigation
- traditional cell culture is no longer widely used
- nuclear acid amplification tests (NAATs) are now the investigation of choice
- urine (first void urine sample), vulvovaginal swab or cervical swab may be tested using the NAAT technique
- for women: the vulvovaginal swab is first-line
- for men: the urine test is first-line
- Chlamydiatesting should be carried out two weeks after a possible exposure

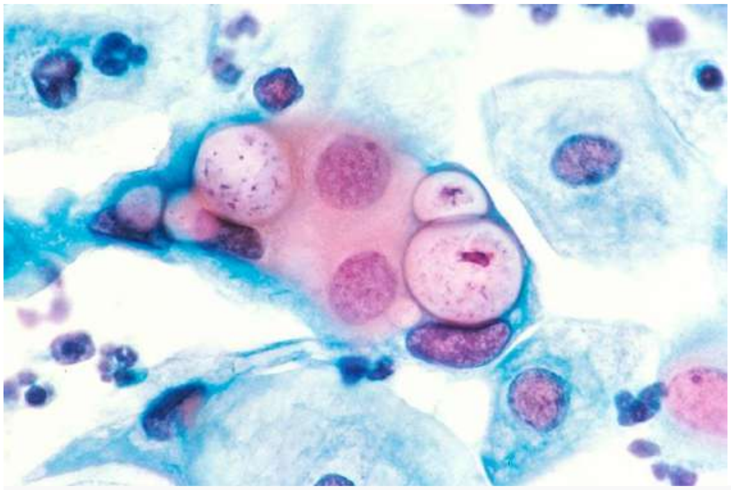
Screening
- in England the National Chlamydia Screening Programme is open to all men and women aged 15-24 years
- the 2009 SIGN guidelines support this approach, suggesting screening all sexually active patients aged 15-24 years
- relies heavily on opportunistic testing



Pap smear demonstrating infected endocervical cells. Red inclusion bodies are typical

Management

- doxycycline (7 day course) or azithromycin (single dose). The 2009 SIGN guidelines suggest azithromycin should be used first-line due to potentially poor compliance with a 7 day course of doxycycline
- if pregnant then azithromycin, erythromycin or amoxicillin may be used. The SIGN guidelines suggest azithromycin 1g stat is the drug of choice 'following discussion of the balance of benefits and risks with the patient'
- patients diagnosed with Chlamydia should be offered a choice of provider for initial partner notification - either trained practice nurses with support from GUM, or referral to GUM
- for men with urethral symptoms: all contacts since, and in the four weeks prior to, the onset of symptoms
- for women and asymptomatic men all partners from the last six months or the most recent sexual partner should be contacted
- contacts of confirmed Chlamydia cases should be offered treatment prior to the results of their investigations being known (treat then test)



Another Pap smear demonstrating infected endocervical cells. Stained with H&E

# LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum (LGV) is caused by Chlamydia trachomatis serovars L1, L2 and L3*.

Risk factors
- men who have sex with men
- the majority of patients who present in developed countries have HIV
- historically was seen more in the tropics

Typically infection comprises of three stages:
- stage 1: small painless pustule which later forms an ulcer
- stage 2: painful inguinal lymphadenopathy
    - may occasionally form fistulating buboes
- stage 3: proctocolitis

LGV is treated using doxycycline.

* 'Normal' Chlamydia resulting in urethritis and pelvic inflammatory disease is caused by Chlamydia trachomatis serovars D through K.

# NON-GONOCOCCAL URETHRITIS

Non-gonococcal urethritis (NGU, sometimes referred to as non-specific urethritis) is a term used to describe the presence of urethritis when a gonococcal bacteria are not identifiable or the initial swab. A typical case would be a male who presented to a GUM clinic with a purulent urethral discharge and dysuria. A swab would be taken in clinic, microscopy performed which showed neutrophils but no Gram negative diplococci (i.e. no evidence of gonorrhoea). Clearly this patient requires immediate treatment prior to waiting for the Chlamydia test to come back and hence an initial diagnosis of NGU is made.

Causative organisms include:
- *Chlamydia trachomatis* - most common cause
- *Mycoplasma genitalium* - thought to cause more symptoms than Chlamydia

Management
- contact tracing
- the BNF and British Association for Sexual Health and HIV (BASHH) both recommend either oral azithromycin or doxycycline

# GONORRHOEA

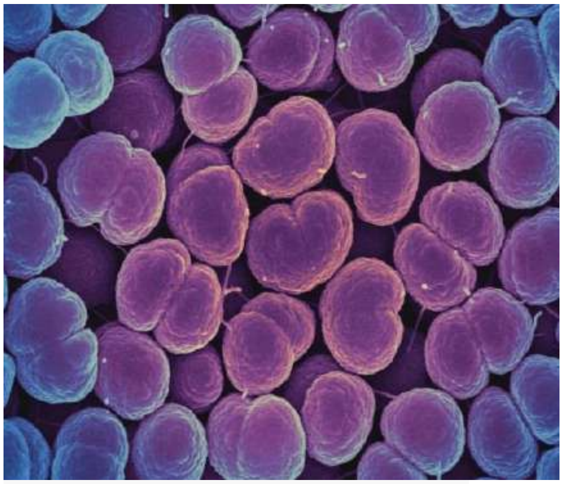
Gonorrhoea is caused by the Gram-negative diplococcus Neisseria gonorrhoeae. Acute infection can occur on any mucous membrane surface, typically genitourinary but also rectum and pharynx. The incubation period of gonorrhoea is 2-5 days

Features
- males: urethral discharge, dysuria
- females: cervicitis e.g. leading to vaginal discharge
- rectal and pharyngeal infection is usually asymptomatic

Microbiology
- immunisation is not possible and reinfection is common due to antigen variation of type IV pili (proteins which adhere to surfaces) and Opa proteins (surface proteins which bind to receptors on immune cells)

Local complications that may develop include urethral strictures, epididymitis and salpingitis (hence may lead to infertility). Disseminated infection may occur - see below

Management
- ciprofloxacin used to be the treatment of choice. However, there is increased resistance to ciprofloxacin (around 36% in the UK) and therefore cephalosporins are now more widely used
- there was a change in the 2019 British Society for Sexual Health and HIV (BASHH) guidelines. Previously the first-line treatment was IM ceftriaxone + oral azithromycin. The new first-line treatment is a single dose of IM ceftriaxone 1g (i.e. no longer add azithromycin). If sensitivities are known (and the organism is sensitive to ciprofloxacin) then a single dose of oral ciprofloxacin 500mg should be given
- if ceftriaxone is refused (e.g. needle-phobic) then oral cefixime 400mg (single dose) + oral azithromycin 2g (single dose) should be used



Colorized scanning electron micrograph of *Neisseria gonorrhoeae*. Credit: NIAID

Disseminated gonococcal infection (DGI) and gonococcal arthritis may also occur, with gonococcal infection being the most common cause of septic arthritis in young adults. The pathophysiology of DGI is not fully understood but is thought to be due to haematogenous spread from mucosal infection (e.g. Asymptomatic genital infection). Initially there may be a classic triad of symptoms: tenosynovitis, migratory polyarthritis and dermatitis. Later complications include septic arthritis, endocarditis and perihepatitis (Fitz-Hugh-Curtis syndrome)

Key features of disseminated gonococcal infection
- tenosynovitis
- migratory polyarthritis
- dermatitis (lesions can be maculopapular or vesicular)

# BACTERIAL VAGINOSIS

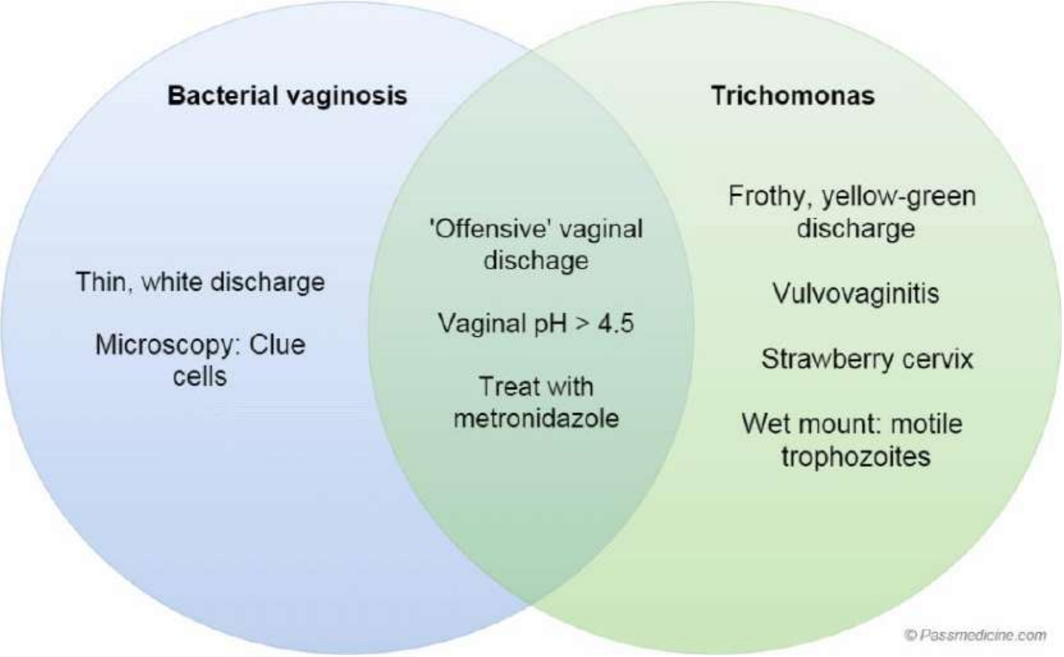
Bacterial vaginosis (BV) describes an overgrowth of predominately anaerobic organisms such as Gardnerella vaginalis. This leads to a consequent fall in lactic acid producing aerobic lactobacilli resulting in a raised vaginal pH.

Whilst BV is not a sexually transmitted infection it is seen almost exclusively in sexually active women.

Features
- vaginal discharge: 'fishy', offensive
- asymptomatic in 50%

Amsel's criteria for diagnosis of BV - 3 of the following 4 points should be present
- thin, white homogenous discharge
- clue cells on microscopy: stippled vaginal epithelial cells
- vaginal pH > 4.5
- positive whiff test (addition of potassium hydroxide results in fishy odour)

Management
- oral metronidazole for 5-7 days
- 70-80% initial cure rate
- relapse rate > 50% within 3 months
- the BNF suggests topical metronidazole or topical clindamycin as alternatives

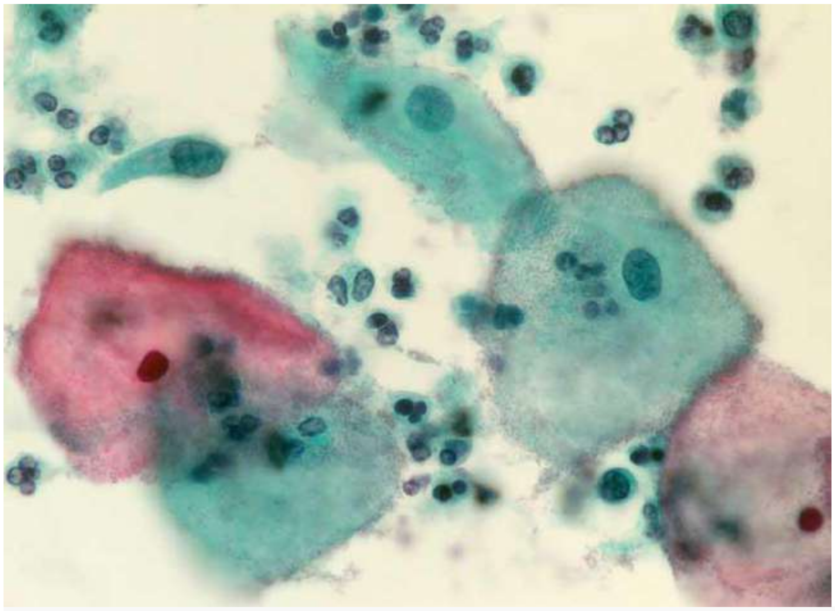


Bacterial vaginosis
Trichomonas
Thin, white discharge
Microscopy: Clue cells
'Offensive' vaginal dischage
Vaginal pH > 4.5
Treat with metronidazole
Frothy, yellow-green discharge
Vulvovaginitis
Strawberry cervix
Wet mount: motile trophozoites
© Passmedicine.com

Comparison of bacterial vaginosis and *Trichomonas vaginalis*

Bacterial vaginosis in pregnancy

- results in an increased risk of preterm labour, low birth weight and chorioamnionitis, late miscarriage
- it was previously taught that oral metronidazole should be avoided in the first trimester and topical clindamycin used instead. Recent guidelines however recommend that oral metronidazole is used throughout pregnancy. The BNF still advises against the use of high dose metronidazole regimes



Clue cells - epithelial cells develop a stippled appearance due to being covered with bacteria

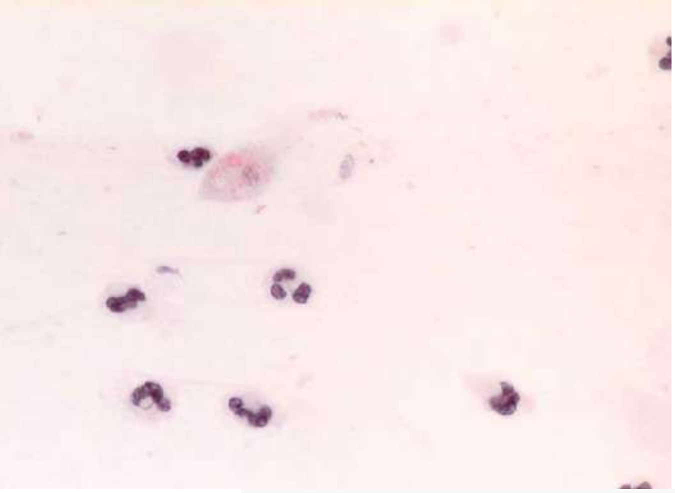
# TRICHOMONAS VAGINALIS

Trichomonas vaginalis is a highly motile, flagellated protozoan parasite. Trichomoniasis is a sexually transmitted infection (STI).

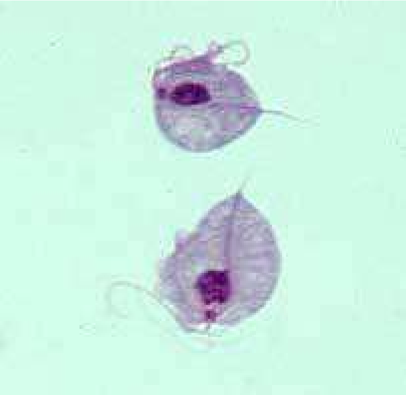
Features
- vaginal discharge: offensive, yellow/green, frothy
- vulvovaginitis
- strawberry cervix
- pH > 4.5
- in men is usually asymptomatic but may cause urethritis

Investigation
- microscopy of a wet mount shows motile trophozoites

Management
- oral metronidazole for 5-7 days, although the BNF also supports the use of a one-off dose of 2g metronidazole



*Trichomonas vaginalis* - largely transparent core with finely granular eosinophilic cytoplasm. Surrounded by neutrophils with segmented nuclei



# URINARY TRACT INFECTION IN ADULTS: MANAGEMENT

**Lower urinary tract infections**

Non-pregnant women

- local antibiotic guidelines should be followed if available
- CKS/2012 SIGN guidelines recommend trimethoprim or nitrofurantoin for 3 days
- send a urine culture if:
  - aged > 65 years
  - visible or non-visible haematuria

Pregnant women

- if the pregnant woman is symptomatic:
  - a urine culture should be sent in all cases
  - should be treated with an antibiotic for
  - first-line: nitrofurantoin (should be avoided near term)
  - second-line: amoxicillin or cefalexin
- asymptomatic bacteriuria in pregnant women:
  - a urine culture should be performed routinely at the first antenatal visit
  - Clinical Knowledge Summaries recommend an immediate antibiotic prescription of either nitrofurantoin (should be avoided near term), amoxicillin or cefalexin. This should be a 7-day course
  - the rationale of treating asymptomatic bacteriuria is the significant risk of progression to acute pyelonephritis
  - a further urine culture should be sent following completion of treatment as a test of cure

Men

- an immediate antibiotic prescription should be offered

Catherised patients

- do not treat asymptomatic bacteria in catheterised patients
- if the patient is symptomatic they should be treated with an antibiotic
  - a 7-day, rather than a 3-day course should be given

**Acute pyelonephritis**

For patients with sign of acute pyelonephritis hospital admission should be considered

- local antibiotic guidelines should be followed if available
- the BNF currently recommends a broad-spectrum cephalosporin or a quinolone (for non-pregnant women) for 10-14 days

# CELLULITIS

Cellulitis is a term used to describe an inflammation of the skin and subcutaneous tissues, typically due to infection by Streptococcus pyogenes or Staphylcoccus aureus.

Features
- commonly occurs on the shins
- erythema, pain, swelling
- there may be some associated systemic upset such as fever

The diagnosis of cellulitis is clinical. No further investigations are required in primary care. Bloods and blood cultures may be requested if the patient is admitted and septicaemia is suspected.

**Criteria for admission**

NICE Clinical Knowledge Summaries recommend we use the Eron classification to guide how we manage patients with cellulitis:

| Class | Features |
|---|---|
| I | There are no signs of systemic toxicity and the person has no uncontrolled co-morbidities |
| II | The person is either systemically unwell or systemically well but with a co-morbidity (for example peripheral arterial disease, chronic venous insufficiency, or morbid obesity) which may complicate or delay resolution of infection |
| III | The person has significant systemic upset such as acute confusion, tachycardia, tachypnoea, hypotension, or unstable co-morbidities that may interfere with a response to treatment, or a limb-threatening infection due to vascular compromize |
| IV | The person has sepsis syndrome or a severe life-threatening infection such as necrotizing fasciitis |

They recommend the following that we admit for intravenous antibiotics the following patients:
- Has Eron Class III or Class IV cellulitis.
- Has severe or rapidly deteriorating cellulitis (for example extensive areas of skin).
- Is very young (under 1 year of age) or frail.
- Is immunocompromized.
- Has significant lymphoedema.
- Has facial cellulitis (unless very mild) or periorbital cellulitis.

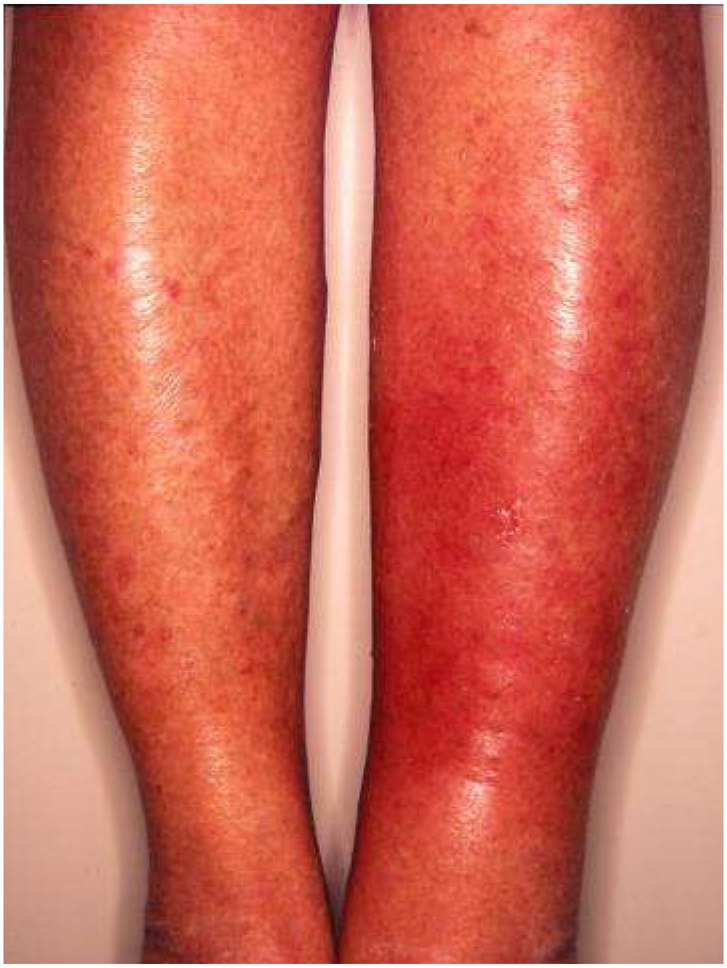
The following is recommend regarding Eron Class II cellulitis:

*Admission may not be necessary if the facilities and expertise are available in the community to give intravenous antibiotics and monitor the person - check local guidelines.*

Other patients can be treated with oral antibiotics.

**Management**
The BNF recommends flucloxacillin as first-line treatment for mild/moderate cellulitis. Clarithromycin, erythromycin (in pregnancy) or doxycyline is recommended in patients allergic to penicillin.

NICE recommend that patients severe cellulitis should be offered co-amoxiclav, cefuroxime, clindamycin or ceftriaxone.



# NECROTISING FASCIITIS

Necrotising fasciitis is a medical emergency that is difficult to recognise in the early stages.

It can be classified according to the causative organism:
- type 1 is caused by mixed anaerobes and aerobes (often occurs post-surgery in diabetics). This is the most common type
- type 2 is caused by Streptococcus pyogenes

Features
- acute onset

- painful, erythematous lesion develops
- often presents as rapidly worsening cellulitis with pain out of keeping with physical features
- extremely tender over infected tissue

Management
- urgent surgical referral debridement
- intravenous antibiotics

# SEPSIS

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to an infection. Sepsis is increasingly recognised as an important cause of mortality in the UK and there has been increasing efforts recently to improve the care of patients who present with sepsis.

How sepsis is classified has changed in recent years - the Surviving Sepsis Guidelines were updated in 2017.

The new guidelines recognise the following terms:

- **sepsis**: life-threatening organ dysfunction caused by a dysregulated host response to infection
- **septic shock**: a more severe form sepsis, technically defined as *'in which circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone'**

The old category of severe sepsis is no longer used.

The term 'systemic inflammatory response syndrome (SIRS)' has also fallen out of favour. Adult patients outside of ICU with suspected infection are identified as being at heightened risk of mortality if they have quickSOFA (qSOFA) score meeting >= 2 of the following criteria: respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100mmHg or less

**qSOFA score**
Respiratory rate > 22/min
Altered mentation
Systolic blood pressure < 100 mm Hg

Within an ICU setting a full SOFA** score is often used. Details can be found at the bottom of the notes.

**Management**
NICE released their own guidelines in 2016. These focussed on the risk stratification and management of patients with suspected.

For risk stratification NICE recommend using the following criteria:

| Red flag criteria | Amber flag criteria |
|---|---|
| • Responds only to voice or pain/ unresponsive | ⍰ Relatives concerned about mental status |
| • Acute confusional state | ⍰ Acute deterioration in functional ability |
| • Systolic B.P <= 90 mmHg (or drop >40 from normal) | ⍰ Immunosuppressed |
| • Heart rate > 130 per minute | ⍰ Trauma/ surgery/ procedure in last 6 weeks |
| • Respiratory rate >= 25 per minute | ⍰ Respiratory rate 21-24 |
| • Needs oxygen to keep SpO2 >=92% | ⍰ Systolic B.P 91-100 mmHg |
| • Non-blanching rash, mottled/ ashen/ cyanotic | ⍰ Heart rate 91-130 OR new dysrhythmia |
| • Not passed urine in last 18 h/ UO < 0.5 ml/kg/hr | ⍰ Not passed urine in last 12-18 hours |

| Red flag criteria | Amber flag criteria |
|---|---|
| • Lactate >=2 mmol/l<br>• Recent chemotherapy | ⍰ Temperature < 36ºC<br>⍰ Clinical signs of wound, device or skin infection |

Clearly the underlying cause of the patients sepsis needs to be identified and treated and the patient supported regardless of the cause or severity. If however any of the red flags are present the 'sepsis six' should be started straight away:

- Administer oxygen: Aim to keep saturations > 94% (88-92% if at risk of CO2 retention e.g. COPD)
- Take blood cultures
- Give broad spectrum antibiotics
- Give intravenous fluid challenges: NICE recommend a bolus of 500ml crystalloid over less than 15 minutes
- Measure serum lactate
- Measure accurate hourly urine output

*these patients can be clinically identified by a vasopressor requirement to maintain a MAP ≥ 65mmHg and serum lactate >2mmol/L in the absence of hypovolemia

**To help identify and categorise patients the Sequential (Sepsis-Related) Organ Failure Assessment Score (SOFA) is increasingly used. The score grades abnormality by organ system and accounts for clinical interventions. However, laboratory variables, namely, PaO2, platelet count, creatinine level, and bilirubin level, are needed for full computation.

**SOFA Score**

| System | Score 0 | Score 1 | Score 2 | Score 3 | Score 4 |
|---|---|---|---|---|---|
| $PaO_2$ /FI $O_2$ | >400 | <400 | <300 | <200 | <100 |
| Platelets x$10^3$ microlitres | >150 | <150 | <100 | <50 | <20 |
| Bilirubin µmol/L | 20 | 20-32 | 33-101 | 102-204 | >204 |
| Cardiovascular | MAP >70mmHg | MAP 70mmHg | Dopamine <5 or dobutamine (any dose) | Dopamine 5.1-15 or epinephrine 0.1 or norepinephrine 0.1 | Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 |
| GCS | 15 | 13-14 | 10-12 | 6-9 | <6 |
| Creatinine µmol/L | <110 | 110-170 | 171-299 | 300-440 | >440 |
| Urine output ml/day | >500 | >500 | >500 | <500 | <200 |

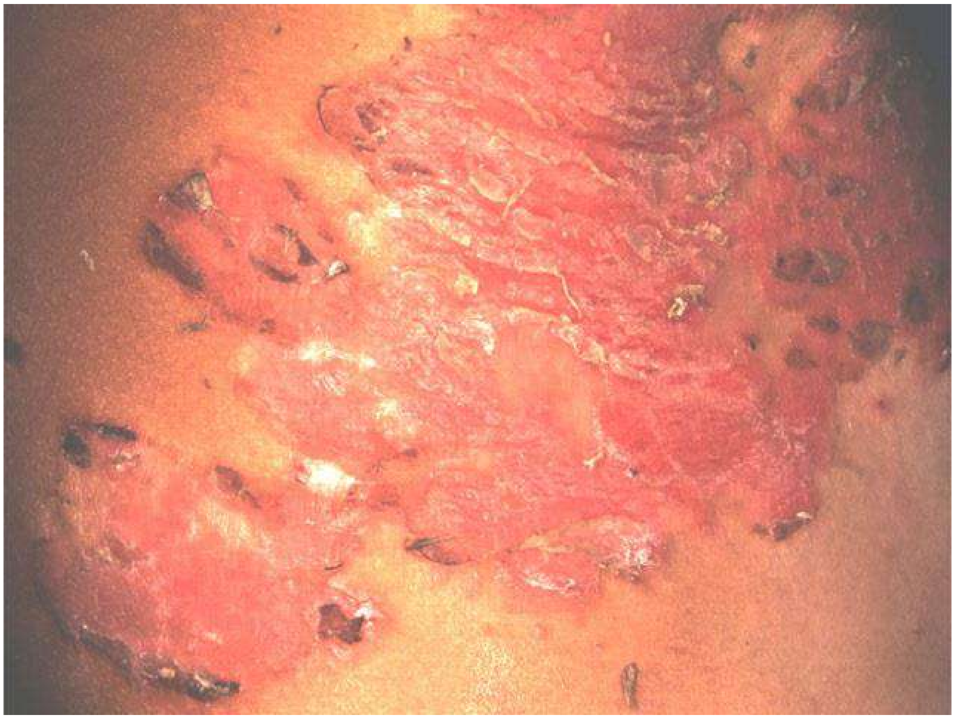
A SOFA score of 2 or more reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.

# STAPHYLOCOCCAL TOXIC SHOCK SYNDROME

Staphylococcal toxic shock syndrome describes a severe systemic reaction to staphylococcal exotoxins. It came to prominence in the early 1980's following a series of cases related to infected tampons

Centers for Disease Control and Prevention diagnostic criteria

- fever: temperature > 38.9ºC
- hypotension: systolic blood pressure < 90 mmHg
- diffuse erythematous rash
- desquamation of rash, especially of the palms and soles
- involvement of three or more organ systems: e.g. gastrointestinal (diarrhoea and vomiting), mucous membrane erythema, renal failure, hepatitis, thrombocytopenia, CNS involvement (e.g. confusion)



# CHICKENPOX EXPOSURE IN PREGNANCY

Chickenpox is caused by primary infection with varicella-zoster virus. Shingles is caused by the reactivation of dormant virus in dorsal root ganglion. In pregnancy, there is a risk to both the mother and also the fetus, a syndrome now termed fetal varicella syndrome

Risks to the mother
- 5 times greater risk of pneumonitis

Fetal varicella syndrome (FVS)
- risk of FVS following maternal varicella exposure is around 1% if occurs before 20 weeks gestation
- studies have shown a very small number of cases occurring between 20-28 weeks gestation and none following 28 weeks
- features of FVS include skin scarring, eye defects (microphthalmia), limb hypoplasia, microcephaly and learning disabilities

Other risks to the fetus
- shingles in infancy: 1-2% risk if maternal exposure in the second or third trimester
- severe neonatal varicella: if the mother develops rash between 5 days before and 2 days after birth there is a risk of neonatal varicella, which may be fatal to the newborn child in around 20% of cases

Management of chickenpox *exposure* in pregnancy
- if there is any doubt about the mother previously having chickenpox maternal blood should be urgently checked for varicella antibodies
- if the pregnant woman is not immune to varicella she should be given varicella-zoster immunoglobulin (VZIG) as soon as possible. RCOG and Greenbook guidelines suggest VZIG is effective up to 10 days post exposure

Management of chickenpox in pregnancy
- if a pregnant woman develops chickenpox in pregnancy then specialist advice should be sought
- there is an increased risk of serious chickenpox infection (i.e. maternal risk) and fetal varicella risk (i.e. fetal risk) balanced against theoretical concerns about the safety of aciclovir in pregnancy
- consensus guidelines (Health Protection Authority and RCOG) suggest oral aciclovir should be given if the pregnant women is ≥ 20 weeks and she presents within 24 hours of onset of the rash
- if the woman is < 20 weeks the aciclovir should be 'considered with caution'

# RUBELLA AND PREGNANCY

Rubella, also known as German measles, is a viral infection caused by the togavirus. Following the introduction of the MMR vaccine it is now rare. If contracted during pregnancy there is a risk of congenital rubella syndrome. Remember that the incubation period is 14-21 days and individuals are infectious from 7 days before symptoms appear to 4 days after the onset of the rash.

Risk
- in first 8-10 weeks risk of damage to fetus is as high as 90%
- damage is rare after 16 weeks

Features of congenital rubella syndrome
- sensorineural deafness
- congenital cataracts
- congenital heart disease (e.g. patent ductus arteriosus)
- growth retardation
- hepatosplenomegaly
- purpuric skin lesions
- 'salt and pepper' chorioretinitis
- microphthalmia
- cerebral palsy

Diagnosis
- suspected cases should be discussed immediately with the local Health Protection Unit (HPU) as type/timing of investigations may vary
- IgM antibodies are raised in women recently exposed to the virus
- it should be noted that it is very difficult to distinguish rubella from parvovirus B19 clinically. It is therefore important to also check parvovirus B19 serology as there is a 30% risk of transplacental infection, with a 5-10% risk of fetal loss

Management
- suspected cases of rubella in pregnancy should be discussed with the local Health Protection Unit
- since 2016, rubella immunity is no longer routinely checked at the booking visit
- if a woman is however tested at any point and no immunity is demonstrated they should be advised to keep away from people who might have rubella
- non-immune mothers should be offered the MMR vaccination in the post-natal period
    - MMR vaccines should not be administered to women known to be pregnant or attempting to become pregnant

# TUBERCULOSIS: FEATURES

Tuberculosis (TB) is the ninth leading cause of death worldwide (WHO). Pulmonary tuberculosis is an infectious disease caused by Mycobacterium tuberculosis. Rarely, it may be due to Mycobacterium bovis or Mycobacterium africanum. In many cases, TB may remain dormant before it progresses to its active form. It most commonly involves the lungs and is communicable in this form, but may affect almost any organ system including the lymph nodes, CNS, liver, bones, genitourinary tract, and gastrointestinal tract.

TB is a notifiable disease.

Epidemiology
- Tuberculosis mostly affects adults in their most productive years.
- Over 95% of cases and deaths are in developing countries
- In the US, an estimated 9.5 million people have latent TB infection

Risk factors - Strong
- Having lived in Asia, Latin America, Eastern Europe, or Africa for years
- Exposure to an infectious TB case
- People who are infected with HIV are 20 to 30 times more likely to develop active TB
- Immunocompromised individuals (diabetics, patients on immunosuppressive therapy, malnourished, or those with haematological malignancies)
- Silicosis
- Apical fibrosis

Risk factors - Weak
- Malignancy
- End-stage renal disease
- IV drug use
- Malnutrition
- Alcoholism
- Diabetes
- Congested residence i.e. nursing homes, homeless shelters etc..
- Smoking

Key diagnostic features:

Common
- Presence of risk factors (see above)
- Cough: initially dry later productive (50% of patients had cough over 2 weeks - 1)
- Low-grade fever. ~20% may have no fever.
- Night sweats, if present usually drenching
- Anorexia
- Malaise ; may only be noticed in hindsight, after treatment

Uncommon

- Pleuritic chest pain
- Haemoptysis ; present in <10% patients (typically with advanced disease) - may be as a result of complication such as bronchiectasis and not representative of active disease.
- Dyspnoea ; a late finding in the setting of extensive lung destruction or effusion
- Weight loss
- Psychological symptoms ; depression or hypomania
- Patient may be asymptomatic and diagnosis made from coincidental findings or screening
- hypoadrenalism

Signs:

- Chest examination may be normal in mild/moderate disease. Possible findings include crackles, bronchial breath sounds, or amphoric breath sounds (distant hollow breath sounds heard over cavities).
- Clubbing - if longstanding disease
- Erythema nodosum

Investigations:

- If there is clinical suspicion of TB, the patient should be isolated
- Chest x-ray: Fibronodular opacities in upper lobes with or without cavitation
- Sputum acid-fast bacilli (AFB) smear (3 sputum samples): Positive for acid-fast bacilli
- Sputum culture: most sensitive and specific test. Should always be performed: positive in TB
- FBC: Raised WBC; low Hb
- Nucleic acid amplification tests (NAAT)(on at least one of the sputum samples): positive for Mycobacterium tuberculosis
- It is recommended that all patients with TB have an HIV test within 2 months of diagnosis of TB
- if the diagnosis is clinical then this should be stated

People who should be screened for TB include those born in high-incidence countries, HIV patients, intravenous drug users, health care workers who serve high-risk populations, and contacts of individuals with pulmonary TB. A tuberculin skin test or interferon gamma release assay are the standard methods for identifying persons infected with the mycobacterium. Screening persons other than high-risk population places a burden on resources and is therefore not recommended.

# TUBERCULOSIS: SCREENING AND DIAGNOSIS

Screening for latent tuberculosis

The Mantoux test is the main technique used to screen for latent tuberculosis. In recent years the interferon-gamma blood test has also been introduced. It is used in a number of specific situations such as:

- the Mantoux test is positive or equivocal
- people where a tuberculin test may be falsely negative (see below)

**Mantoux test**

- 0.1 ml of 1:1,000 purified protein derivative (PPD) injected intradermally
- result read 2-3 days later
  -

| Diameter of induration | Positivity | Interpretation |
|---|---|---|
| < 6mm | Negative - no significant hypersensitivity to tuberculin protein | Previously unvaccinated individuals may be given the BCG |
| 6 - 15mm | Positive - hypersensitive to tuberculin protein | Should not be given BCG. May be due to previous TB infection or BCG |
| > 15mm | Strongly positive - strongly hypersensitive to tuberculin protein | Suggests tuberculosis infection. |

False negative tests may be caused by:

- miliary TB
- sarcoidosis
- HIV
- lymphoma
- very young age (e.g. < 6 months)

**Heaf test**

The Heaf test was previously used in the UK but has been since been discontinued. It involved injection of PPD equivalent to 100,000 units per ml to the skin over the flexor surface of the left forearm. It was then read 3-10 days later.

**Diagnosis of active tuberculosis**

Chest x-ray

- upper lobe cavitation is the classical finding of reactivated TB
- bilateral hilar lymphadenopathy

Sputum smear

- 3 specimens are needed
- rapid and inexpensive test
- stained for the presence of acid-fast bacilli (Ziehl-Neelsen stain)
  - all mycobacteria will stain positive (i.e. nontuberculous mycobacteria)
- the sensitivity is between 50-80%
  - this is decreased in individuals with HIV to around 20-30%

Sputum culture

- the gold standard investigation
  - more sensitive than a sputum smear and nucleic acid amplification tests

  - can assess drug sensitivities
- can take 1-3 weeks (if using liquid media, longer if solid media)

Nucleic acid amplification tests (NAAT)
- allows rapid diagnosis (within 24-48 hours)
- more sensitive than smear but less sensitive than culture

# TUBERCULOSIS: DRUG THERAPY

The standard therapy for treating active tuberculosis is:

Initial phase - first 2 months (RIPE)
- Rifampicin
- Isoniazid
- Pyrazinamide
- Ethambutol (the 2006 NICE guidelines now recommend giving a 'fourth drug' such as ethambutol routinely - previously this was only added if drug-resistant tuberculosis was suspected)

Continuation phase - next 4 months
- Rifampicin
- Isoniazid

The treatment for **latent tuberculosis** is 3 months of isoniazid (with pyridoxine) and rifampicin OR 6 months of isoniazid (with pyridoxine)

Patients with **meningeal tuberculosis** are treated for a prolonged period (at least 12 months) with the addition of steroids

**Directly observed therapy** with a three times a week dosing regimen may be indicated in certain groups, including:
- homeless people with active tuberculosis
- patients who are likely to have poor concordance
- all prisoners with active or latent tuberculosis

# LEPROSY

Leprosy is a granulomatous disease primarily affecting the peripheral nerves and skin. It is caused by Mycobacterium leprae.

Features

- patches of hypopigmented skin typically affecting the buttocks, face, and extensor surfaces of limbs
- sensory loss

The degree of cell mediated immunity determines the type of leprosy a patient will develop.

Low degree of cell mediated immunity → lepromatous leprosy ('multibacillary')
- extensive skin involvement
- symmetrical nerve involvement

High degree of cell mediated immunity → tuberculoid leprosy ('paucibacillary')
- limited skin disease
- asymmetric nerve involvement → hypesthesia
- hair loss

Management
- WHO-recommended triple therapy: rifampicin, dapsone and clofazimine

# RESPIRATORY PATHOGENS

The table below lists the more common respiratory pathogens:

| Pathogen | Associated condition |
|---|---|
| Respiratory syncytial virus | Bronchiolitis |
| Parainfluenza virus | Croup |
| Rhinovirus | Common cold |
| Influenza virus | Flu |
| *Streptococcus pneumoniae* | The most common cause of community-acquired pneumonia |
| *Haemophilus influenzae* | Community-acquired pneumonia<br>Most common cause of bronchiectasis exacerbations<br>Acute epiglottitis |
| *Staphylococcus aureus* | Pneumonia, particularly following influenza |
| *Mycoplasma pneumoniae* | Atypical pneumonia<br>Flu-like symptoms classically precede a dry cough. Complications include haemolytic anaemia and erythema multiforme |
| *Legionella pneumophilia* | Atypical pneumonia<br>Classically spread by air-conditioning systems, causes dry cough. Lymphopenia, deranged liver function tests and hyponatraemia may be seen |
| Pneumocystis jiroveci | Common cause of pneumonia in HIV patients. Typically patients have few chest signs and develop exertional dyspnoea |
| *Mycobacterium tuberculosis* | Causes tuberculosis. A wide range of presentations from asymptomatic to disseminated disease are possible. Cough, night sweats and weight loss may be seen |

# PNEUMONIA: CAUSES

Community acquired pneumonia (CAP) may be caused by the following infectious agents:

- *Streptococcus pneumoniae* (accounts for around 80% of cases)
- *Haemophilus influenzae*
- *Staphylococcus aureus*: commonly after the 'flu
- atypical pneumonias (e.g. Due to *Mycoplasma pneumoniae*)
- viruses

Klebsiella pneumoniae is classically in alcoholics

***Streptococcus pneumoniae (pneumococcus)*** is the most common cause of community-acquired pneumonia

Characteristic features of pneumococcal pneumonia
- rapid onset
- high fever
- pleuritic chest pain
- herpes labialis

# CEPHALOSPORINS

Cephalosporins are a type of β-lactam antibiotic which are bactericidal. They are less susceptible to penicillinases than penicillins.

β-lactam antibiotics work by disrupting the synthesis of bacterial cell walls, by inhibiting peptidoglycan cross-linking.

Mechanism of resistance
- Changes to penicillin-binding-proteins (PBPs), which are types of transpeptidases (enzymes produced by bacteria that cross-links peptidoglycan chains to form rigid cell walls)

# LEGIONELLA

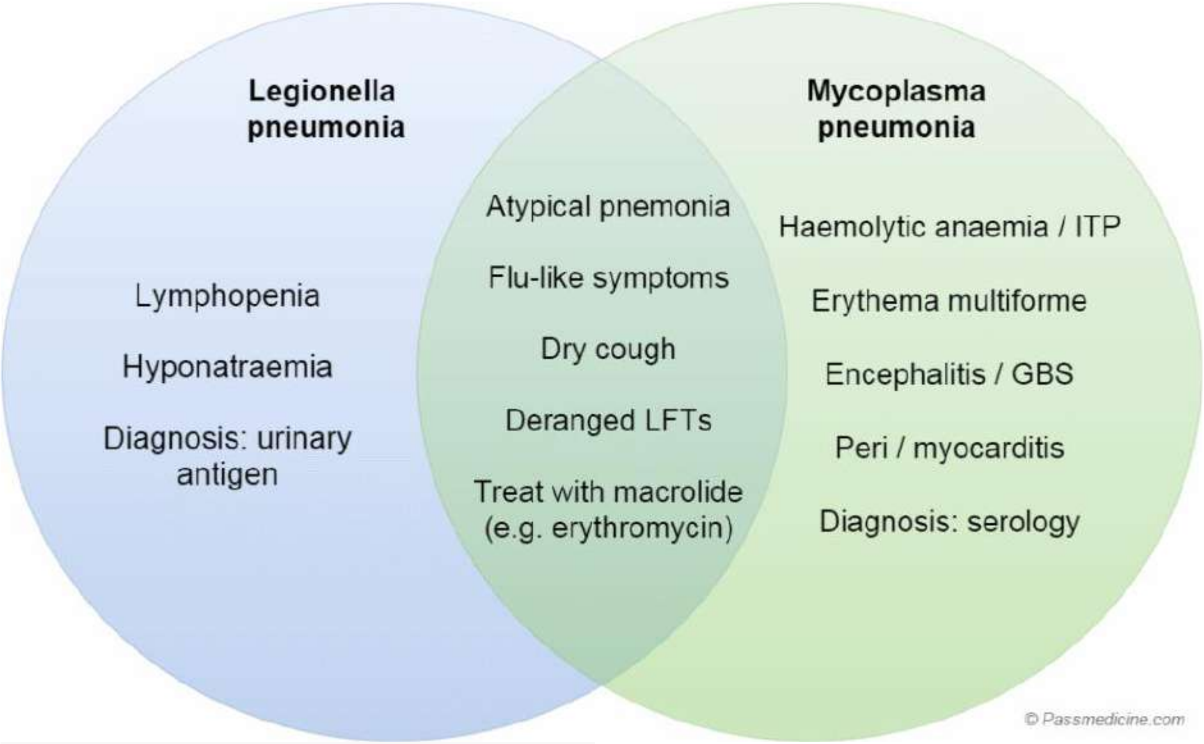
Legionnaire's disease is caused by the intracellular bacterium Legionella pneumophilia. It typically colonizes water tanks and hence questions may hint at air-conditioning systems or foreign holidays. Person-to-person transmission is not seen

Features
- flu-like symptoms including fever (present in > 95% of patients)
- dry cough
- relative bradycardia
- confusion
- lymphopaenia
- hyponatraemia
- deranged liver function tests
- pleural effusion: seen in around 30% of patients

Diagnosis
- urinary antigen

Management

- treat with erythromycin/clarithromycin


Legionella pneumonia
Lymphopenia
Hyponatraemia
Diagnosis: urinary antigen
Atypical pnemonia
Flu-like symptoms
Dry cough
Deranged LFTs
Treat with macrolide (e.g. erythromycin)
Mycoplasma pneumonia
Haemolytic anaemia / ITP
Erythema multiforme
Encephalitis / GBS
Peri / myocarditis
Diagnosis: serology
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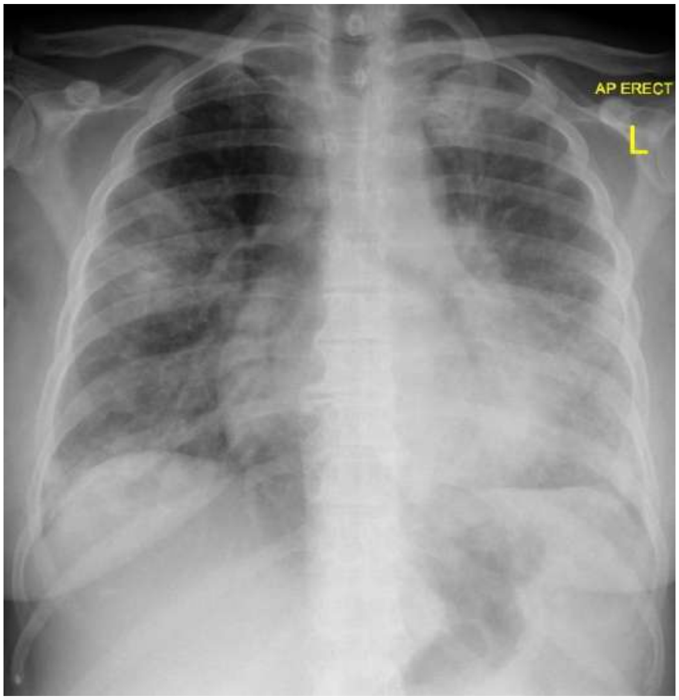
Comparison of Legionella and Mycoplasma pneumonia



Chest x-ray features of legionella pnuemonia are non-specific but includes a mid-to-lower zone predominance of patchy consolidation. Pleural effusions are seen in around 30%.

# MYCOPLASMA PNEUMONIAE

Mycoplasma pneumoniae is a cause of atypical pneumonia which often affects younger patients. It is associated with a number of characteristic complications such as erythema multiforme and cold autoimmune haemolytic anaemia. Epidemics of Mycoplasma pneumoniae classically occur every 4 years. It is important to recognise atypical pneumonia as it may not respond to penicillins or cephalosporins due to it lacking a peptidoglycan cell wall.

Features
- the disease typically has a prolonged and gradual onset
- flu-like symptoms classically precede a dry cough
- bilateral consolidation on x-ray
- complications may occur as below

Complications
- cold agglutins (IgM): may cause an haemolytic anaemia, thrombocytopenia
- erythema multiforme, erythema nodosum
- meningoencephalitis, Guillain-Barre syndrome and other immune-mediated neurological diseases
- bullous myringitis: painful vesicles on the tympanic membrane
- pericarditis/myocarditis
- gastrointestinal: hepatitis, pancreatitis
- renal: acute glomerulonephritis

Investigations
- diagnosis is generally by Mycoplasma serology
- positive cold agglutination test

Management
- doxycycline or a macrolide (e.g. erythromycin/clarithromycin)

# INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis (glandular fever) (EBV, also known as human herpesvirus 4, HHV-4) in 90% of cases. Less frequent causes include cytomegalovirus and HHV-6. It is most common in adolescents and young adults.

The classic triad of sore throat, pyrexia and lymphadenopathy is seen in around 98% of patients:
- sore throat
- lymphadenopathy: may be present in the anterior and posterior triangles of the neck, in contrast to tonsillitis which typically only results in the upper anterior cervical chain being enlarged

- pyrexia

Other features include:
- malaise, anorexia, headache
- palatal petechiae
- splenomegaly - occurs in around 50% of patients and may rarely predispose to splenic rupture
- hepatitis, transient rise in ALT
- lymphocytosis: presence of 50% lymphocytes with at least 10% atypical lymphocytes
- haemolytic anaemia secondary to cold agglutins (IgM)
- a maculopapular, pruritic rash develops in around 99% of patients who take ampicillin/amoxicillin whilst they have infectious mononucleosis

Symptoms typically resolve after 2-4 weeks.

Diagnosis
- heterophil antibody test (Monospot test) - NICE guidelines suggest FBC and Monospot in the 2nd week of the illness to confirm a diagnosis of glandular fever.

Management is supportive and includes:
- rest during the early stages, drink plenty of fluid, avoid alcohol
- simple analgesia for any aches or pains
- consensus guidance in the UK is to avoid playing contact sports for 8 weeks after having glandular fever to reduce the risk of splenic rupture

There is an interesting correlation between EBV and socioeconomic groups. Lower socioeconomic groups have high rates of EBV seropositivity, having frequently acquired EBV in early childhood when the primary infection is often subclinical. However, higher socioeconomic groups show a higher incidence of infectious mononucleosis, as acquiring EBV in adolescence or early adulthood results in symptomatic disease.

# GASTROENTERITIS: CAUSES

Gastroenteritis may either occur whilst at home or whilst travelling abroad (travellers' diarrhoea)

Travellers' diarrhoea may be defined as at least 3 loose to watery stools in 24 hours with or without one of more of abdominal cramps, fever, nausea, vomiting or blood in the stool. The most common cause is Escherichia coli.

Another pattern of illness is 'acute food poisoning'. This describes the sudden onset of nausea, vomiting and diarrhoea after the ingestion of a toxin. Acute food poisoning is typically caused by Staphylococcus aureus, Bacillus cereus or Clostridium perfringens.

**Stereotypical histories**

| Infection | Typical presentation |
|---|---|
| ***Escherichia coli*** | Common amongst travellers<br>Watery stools<br>Abdominal cramps and nausea |
| **Giardiasis** | Prolonged, non-bloody diarrhoea |
| **Cholera** | Profuse, watery diarrhoea<br>Severe dehydration resulting in weight loss<br>Not common amongst travellers |
| ***Shigella*** | Bloody diarrhoea<br>Vomiting and abdominal pain |
| ***Staphylococcus aureus*** | Severe vomiting<br>Short incubation period |
| ***Campylobacter*** | A flu-like prodrome is usually followed by crampy abdominal pains, fever and diarrhoea which may be bloody<br>May mimic appendicitis<br>Complications include Guillain-Barre syndrome |
| ***Bacillus cereus*** | Two types of illness are seen<br>• vomiting within 6 hours, stereotypically due to rice<br>• diarrhoeal illness occurring after 6 hours |
| **Amoebiasis** | Gradual onset bloody diarrhoea, abdominal pain and tenderness which may last for several weeks |

Incubation period

- 1-6 hrs: Staphylococcus aureus, Bacillus cereus*
- 12-48 hrs: Salmonella, Escherichia coli
- 48-72 hrs: Shigella, Campylobacter
- > 7 days: Giardiasis, Amoebiasis

*vomiting subtype, the diarrhoeal illness has an incubation period of 6-14 hours

## AMOEBIASIS

Amoebiasis is caused by Entamoeba histolytica (an amoeboid protozoan) and spread by the faecal-oral route. It is estimated that 10% of the world's population is chronically infected. Infection can be asymptomatic, cause mild diarrhoea or severe amoebic dysentery. Amoebiasis also causes liver and colonic abscesses.

Amoebic dysentery
- profuse, bloody diarrhoea
- there may be a long incubation period
- stool microscopy may show trophozoites if examined within 15 minutes or kept warm (known as a 'hot stool')
- treatment is with metronidazole

Amoebic liver abscess
- usually a single mass in the right lobe (may be multiple). The contents are often described as 'anchovy sauce'
- features: fever, RUQ pain
- serology is positive in > 90%

Treatment for invasive amoebiasis should be followed by a luminal amoebicide to eradicate the cystic stage which is resistant to metronidazole and tinidazole (which are used against the invasive stage).

## GIARDIASIS

Giardiasis is caused by the flagellate protozoan Giardia lamblia. It is spread by the faeco-oral route

Features
- often asymptomatic
- lethargy, bloating, abdominal pain
- flatulence
- non-bloody diarrhoea
- chronic diarrhoea, malabsorption and lactose intolerance can occur
- stool microscopy for trophozoite and cysts are classically negative, therefore duodenal fluid aspirates or 'string tests' (fluid absorbed onto swallowed string) are sometimes needed

Treatment is with metronidazole.

## METRONIDAZOLE

Metronidazole is a type of antibiotic that works by forming reactive cytotoxic metabolites inside the bacteria.

Adverse effects
- disulfiram-like reaction with alcohol

## SHIGELLA

Overview
- causes diarrhoea (may be bloody), abdominal pain
- severity depends on type: S sonnei (e.g. from UK) may be mild, S. flexneri or S. dysenteriae from abroad may cause severe disease
- Shigella infection is usually self-limiting and does not require antibiotic treatment
- antibiotics (e.g. ciprofloxacin) are indicated for people with severe disease, who are immunocompromised or with bloody diarrhoea

## CHOLERA

Overview
- caused by Vibro cholerae - Gram negative bacteria

Features
- profuse 'rice water' diarrhoea
- dehydration
- hypoglycaemia

Management
- oral rehydration therapy
- antibiotics: doxycycline, ciprofloxacin

## NOROVIRUS

Norovirus, also known as the winter vomiting bug, is one of the most common causes of gastroenteritis in the UK according to NHS England. It is a genus that encompasses a range of non encapsulated RNA virus species. The CDC (Centre for Disease Prevention and Control) estimates that

1 in 5 cases of infectious gastroenteritis are caused by norovirus, with 685 million cases per year worldwide.

Symptoms

- Develop within 15 - 50 hours of infection (quoted from the European Centre of Disease Control and Prevention), with patients experiencing nausea, vomiting, and diarrhoea, which may be accompanied by headaches, low-grade fevers, and myalgia.
- The majority of patients experience both vomiting and diarrhoea
- 10 - 22% reported a headache and up to 47% of patients reported fevers (Clinical Microbiology Reviews, Norovirus, January 2015)

Transmission

- Faecal-oral route, with the virus becoming aerosolized when the patient vomits or when a toilet containing infected bodily fluids (vomit or faeces) is flushed.
- Viral particles are transmitted directly to surrounding potential hosts and to surrounding surfaces, from which they can be transmitted by cross-contamination (for example a patient visitor touching the patient environment, then eating without first washing their hands).
- Infection may also be transmitted from an infected individual in the process of direct physical contact, or contact with food preparation.
- The virus enters the cell via host receptor-mediated endocytosis and replicates in the small intestine. Norovirus is highly contagious, the European Centre of Disease Control and Prevention estimates that only 10 - 100 viral particles are required to cause an active infection.
- Norovirus is not at present considered to be a notifiable disease in the UK.

Limiting transmission

- Isolation of infected strongly recommended where possible, particularly in areas where the risk of person to person transmission is high, for example, in hospitals schools, and care facilities
- Good hand hygiene using soap and water is essential
- Alcohol hand gel has been shown to be less effective in reducing transmission

Diagnosis

- Clinical history and stool culture viral PCR (polymerase chain reaction).

Differential diagnoses

- Features most suggestive of norovirus include sudden onset vomiting, relatively short duration of symptoms and contact with others with similar symptoms.
- Rotavirus, E. coli and Salmonella infections will all cause similar clinical pictures, however, there are some important differentiating features.
- Salmonella infection has an incubation period of 6 - 72 hours and is often the result of contact with contaminated animal products, for example, unpasteurized eggs or milk. Unlike norovirus, salmonella gastroenteritis can cause bloody diarrhoea and patients often have a high fever.
- Rotavirus gastroenteritis causes symptoms very similar to those of norovirus, but predominantly affects children under the age of 5 years.

- E. coli infection, like Norovirus, causes vomiting and diarrhoea but has a longer incubation period (between 3-4 days but can be up to 10 days following pathogen exposure) and unlike Norovirus, E Coli infection commonly causes severe abdominal cramping and frequently causes bloody diarrhoea.

Resolution and Potential Complications

- The infection is self-limiting in immunocompetent patients and symptoms generally resolve within 72 hours
- Dehydration and electrolyte imbalances may arise as a result of vomiting and diarrhoea, leading to significant morbidity and mortality and patients should be managed supportively with rehydration and electrolyte supplementation where necessary.

# MRSA

Methicillin-resistant Staphylococcus aureus (MRSA) was one of the first organisms which highlighted the dangers of hospital-acquired infections.

Who should be screened for MRSA?

- all patients awaiting elective admissions (exceptions include day patients having terminations of pregnancy and ophthalmic surgery. Patients admitted to mental health trusts are also excluded)
- from 2011 all emergency admissions will be screened

How should a patient be screened for MRSA?

- nasal swab and skin lesions or wounds
- the swab should be wiped around the inside rim of a patient's nose for 5 seconds
- the microbiology form must be labelled 'MRSA screen'

Suppression of MRSA from a carrier once identified

- nose: mupirocin 2% in white soft paraffin, tds for 5 days
- skin: chlorhexidine gluconate, od for 5 days. Apply all over but particularly to the axilla, groin and perineum

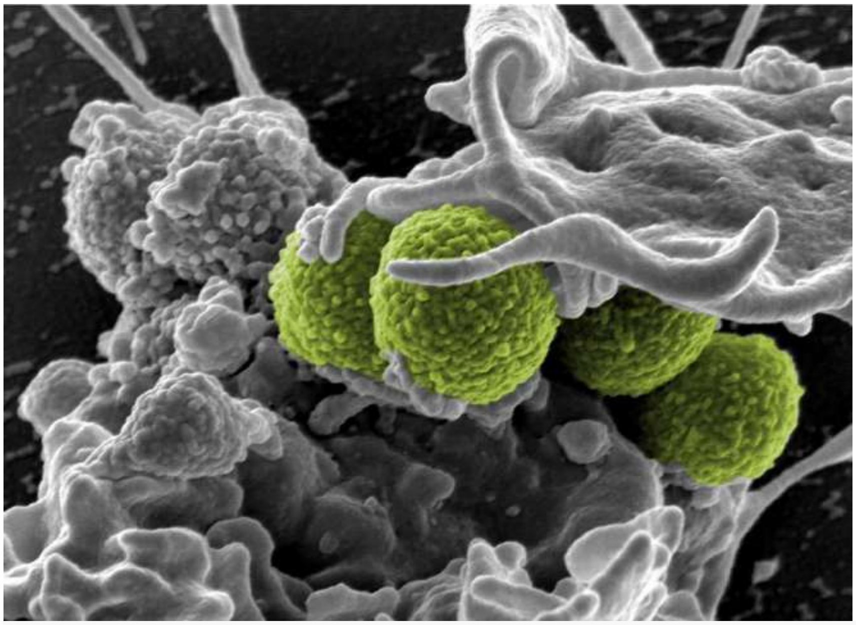
The following antibiotics are commonly used in the treatment of MRSA infections:

- vancomycin
- teicoplanin
- linezolid

Some strains may be sensitive to the antibiotics listed below but they should not generally be used alone because resistance may develop:

- rifampicin
- macrolides
- tetracyclines
- aminoglycosides
- clindamycin

Relatively new antibiotics such as linezolid, quinupristin/dalfopristin combinations and tigecycline have activity against MRSA but should be reserved for resistant cases



Interaction of MRSA (green bacteria) with a human white cell. The bacteria shown is strain MRSA252, a leading cause of hospital-associated infections in the United States and United Kingdom. Credit: NIAID

## VANCOMYCIN

Vancomycin is a glycopeptide antibiotic used in the treatment of Gram-positive infections, particularly methicillin-resistant Staphylococcus aureus (MRSA).

Mechanism of action
- inhibits cell wall formation by binding to D-Ala-D-Ala moieties, preventing polymerization of peptidoglycans

Mechanism of resistance
- alteration to the terminal amino acid residues of the NAM/NAG-peptide subunits (normally D-alanyl-D-alanine) to which the antibiotic binds

Adverse effects
- nephrotoxicity
- ototoxicity
- thrombophlebitis
- red man syndrome; occurs on rapid infusion of vancomycin

## LINEZOLID

Linezolid is a type of oxazolidonone antibiotic which has been introduced in recent years. It inhibits bacterial protein synthesis by stopping formation of the 70s initiation complex and is bacteriostatic nature

Spectrum, highly active against Gram positive organisms including:

- MRSA (Methicillin-resistant Staphylococcus aureus)
- VRE (Vancomycin-resistant enterococcus)
- GISA (Glycopeptide Intermediate Staphylococcus aureus)

Adverse effects

- thrombocytopenia (reversible on stopping)
- monoamine oxidase inhibitor: avoid tyramine containing foods

# BOTULISM

*Clostridium botulinum*

- gram positive anaerobic bacillus
- 7 serotypes A-G
- produces botulinum toxin, a neurotoxin which irreversibly blocks the release of acetylcholine
- may result from eating contaminated food (e.g. tinned) or intravenous drug use
- neurotoxin often affects bulbar muscles and autonomic nervous system

Features

- patient usually fully conscious with no sensory disturbance
- flaccid paralysis
- diplopia
- ataxia
- bulbar palsy

Treatment

- botulism antitoxin and supportive care
    - antitoxin is only effective if given early - once toxin has bound its actions cannot be reversed

# MENINGITIS: CAUSES

0 - 3 months

- *Group B Streptococcus (most common cause in neonates)*
- *E. coli*
- *Listeria monocytogenes*

3 months - 6 years

- *Neisseria meningitidis*
- *Streptococcus pneumoniae*
- *Haemophilus influenzae*

6 years - 60 years

- *Neisseria meningitidis*
- *Streptococcus pneumoniae*

> 60 years

- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Listeria monocytogenes*

Immunosuppressed

- *Listeria monocytogenes*

# MENINGITIS: CSF ANALYSIS

The table below summarises the characteristic cerebrospinal fluid (CSF) findings in meningitis:

| | Bacterial | Viral | Tuberculous | Fungal |
|---|---|---|---|---|
| **Appearance** | Cloudy | Clear/cloudy | Slight cloudy, fibrin web | Cloudy |
| **Glucose** | Low (< 1/2 plasma) | 60-80% of plasma glucose* | Low (< 1/2 plasma) | Low |
| **Protein** | High (> 1 g/l) | Normal/raised | High (> 1 g/l) | High |
| **White cells** | 10 - 5,000 polymorphs/mm³ | 15 - 1,000 lymphocytes/mm³ | 30 - 300 lymphocytes/mm³ | 20 - 200 lymphocytes/mm³ |

The Ziehl-Neelsen stain is only 20% sensitive in the detection of tuberculous meningitis and therefore PCR is sometimes used (sensitivity = 75%)

*mumps is unusual in being associated with a low glucose level in a proportion of cases. A low glucose may also be seen in herpes encephalitis

# MENINGITIS: MANAGEMENT

Investigations suggested by NICE

- full blood count
- CRP
- coagulation screen
- blood culture
- whole-blood PCR
- blood glucose
- blood gas

Lumbar puncture if no signs of raised intracranial pressure

**Management**

All patients should be transferred to hospital urgently. If patients are in a pre-hospital setting (for example a GP surgery) and meningococcal disease is suspected then intramuscular benzylpenicillin may be given, as long as this doesn't delay transit to hospital.

BNF recommendations on antibiotics

| Scenario | BNF recommendation |
|---|---|
| Initial empirical therapy aged < 3 months | Intravenous cefotaxime + amoxicillin |
| Initial empirical therapy aged 3 months - 50 years | Intravenous cefotaxime* |
| Initial empirical therapy aged > 50 years | Intravenous cefotaxime + amoxicillin |
| Meningococcal meningitis | Intravenous benzylpenicillin or cefotaxime |
| Pneuomococcal meningitis | Intravenous cefotaxime |
| Meningitis caused by *Haemophilus influenzae* | Intravenous cefotaxime |
| Meningitis caused by Listeria | Intravenous amoxicillin + gentamicin |

Intravenous dexamethasone should also be given to reduce the risk of neurological sequelae.

If the patient has a history of immediate hypersensitivity reaction to penicillin or to cephalosporins the BNF recommends using chloramphenicol.

Management of contacts

- prophylaxis needs to be offered to household and close contacts of patients affected with meningococcal meningitis. Prophylaxis should also be offered to people who been exposed to respiratory secretion, regardless of the closeness of contact
- people who have been exposed to a patient with confirmed bacterial meningitis should be given prophylactic antibiotics if they have close contact within the 7 days before onset

- oral ciprofloxacin or rifampicin or may be used. The Health Protection Agency (HPA) guidelines now state that whilst either may be used ciprofloxacin is the drug of choice as it is widely available and only requires one dose
- the risk is highest in the first 7 days but persists for at least 4 weeks
- meningococcal vaccination should be offered to close contacts when serotype results are available, including booster doses to those who had the vaccine in infancy
- for pneumococcal meningitis, no prophylaxis is generally needed. There are however exceptions to this. If a cluster of cases of pneumococcal meningitis occur the HPA have a protocol for offering close contacts antibiotic prophylaxis. Please see the link for more details

*in the 2015 update of the NICE *Meningitis (bacterial) and meningococcal septicaemia in under 16s: recognition, diagnosis and management* the recommendation for initial empirically therapy for children > than 3 months is intravenous ceftriaxone

## MENINGOCOCCAL SEPTICAEMIA: INVESTIGATIONS

Meningococcal septicaemia is a frightening condition for patients, parents and doctors. It is associated with a high morbidity and mortality unless treated early - meningococcal disease is the leading infectious cause of death in early childhood. A high index of suspicion is therefore needed. Much of the following is based on the 2010 NICE guidelines (please see link).

Presentation of meningococcal disease:
- 15% - meningitis
- 25% - septicaemia
- 60% - a combination of meningitis and septicaemia

Investigations
- blood cultures
- blood PCR
- lumbar puncture is usually contraindicated
- full blood count and clotting to assess for disseminated intravascular coagulation

# LISTERIA

Listeria monocytogenes is a Gram-positive bacillus which has the unusual ability to multiply at low temperatures. It is typically spread via contaminated food, typically unpasteurised dairy products. Infection is particularly dangerous to the unborn child where it can lead to miscarriage.

Features - can present in a variety of ways
- diarrhoea, flu-like illness
- pneumonia , meningoencephalitis
- ataxia and seizures

Suspected Listeria infection should be investigated by taking blood cultures. CSF may reveal a pleocytosis, with 'tumbling motility' on wet mounts

Management
- Listeria is sensitive to amoxicillin/ampicillin (cephalosporins usually inadequate)
- Listeria meningitis should be treated with IV amoxicillin/ampicillin and gentamicin

In pregnant women
- pregnant women are almost 20 times more likely to develop listeriosis compared with the rest of the population due to changes in the immune system
- fetal/neonatal infection can occur both transplacentally and vertically during child birth
- complications include miscarriage, premature labour, stillbirth and chorioamnionitis
- diagnosis can only be made from blood cultures
- treatment is with amoxicillin

# TETANUS

Tetanus is caused by the tetanospasmin exotoxin released from Clostridium tetani. Tetanus spores are present in soil and may be introduced into the body from a wound, which is often unnoticed. Tetanospasmin prevents release of GABA

Features
- prodrome fever, lethargy, headache
- trismus (lockjaw)
- risus sardonicus
- opisthotonus (arched back, hyperextended neck)
- spasms (e.g. dysphagia)

Management
- supportive therapy including ventilatory support and muscle relaxants

- intramuscular human tetanus immunoglobulin for high-risk wounds (e.g. compound fractures, delayed surgical intervention, significant degree of devitalised tissue)
- metronidazole is now preferred to benzylpenicillin as the antibiotic of choice

# DIPHTHERIA

Diphtheria is caused by the Gram positive bacterium Corynebacterium diphtheriae

Pathophysiology
- releases an exotoxin encoded by a β-prophage
- exotoxin inhibits protein synthesis by catalyzing ADP-ribosylation of elongation factor EF-2

Diphtheria toxin commonly causes a 'diphtheric membrane' on tonsils caused by necrotic mucosal cells. Systemic distribution may produce necrosis of myocardial, neural and renal tissue

Possible presentations
- recent visitors to Eastern Europe/Russia/Asia
- sore throat with a 'diphtheric membrane' - see above
- bulky cervical lymphadenopathy
- neuritis e.g. cranial nerves
- heart block

# MELIOIDOSIS

Melioidosis, also called Whitmore's disease, is an infection caused by the gram-negative bacteriumBurkholderia pseudomallei. This organism is a widely distributed environmental saprophyte in soil and fresh surface water in endemic regions.

Epidemiology:
- Endemic in tropics and subtropics climates, mainly in Southeast Asia (e.g Thailand, Malaysia) and Northern America.
- 150,000 case/year worldwide, with most cases occurring in wet seasons.

Transmission:
- Percutaneous inoculation: contact with contaminated soil or water (most common)
- Inhalation, aspiration, or ingestion of contaminated dust or water
- Person-to-person transmission is rare

Risk factors:
- Diabetes mellitus (the strongest risk factor)

- Chronic renal, liver, or lung disease (e.g., cystic fibrosis)
- Immunocompromised states (e.g., malignancy, long-term glucocorticoid use)
- Occupational exposure: agricultural work

Sign and symptoms:
- Incubation period: 1-21 days ( mean around 9 days)
- Symptomatic cases can be acute, chronic (> 2 months), or reactivations of latent infection.
- Clinical features depend on the infected organ:

Acute pulmonary infection (most common): wide range of presentations (mild to severe)
- Localized infection: skin ulcer, nodule, or abscess.
- Visceral abscesses: especially in the prostate, spleen, kidney, and liver.
- Disseminated infection: occurs in ∼ 55% of cases and has a 20% mortality rate. Manifests with fever and septic shock.

Diagnosis:
- Culture: the mainstay of diagnosis. Gram stain of sputum or abscess pus
- Imaging: Chest radiography: may show signs of acute pneumonia

Treatment:
- Initial intensive therapy: IV ceftazidime, imipenem, or meropenem for 10–14 days
- Followed by eradication therapy: oral TMP/SMX (plus doxycycline) for 3–6 months
- Adjunct therapy: abscess drainage.

Prevention:
- In endemic areas, contact with soil and standing water should be avoided (e.g., agricultural workers should wear boots)
- Health care and laboratory workers should wear masks, gloves, and gowns to prevent infection.
- No vaccination available

# LEMIERRE'S SYNDROME

Lemierre's syndrome is an infectious thrombophlebitis of the internal jugular vein.

It most often occurs secondary to a bacterial sore throat caused by Fusobacterium necrophorum leading to a peritonsillar abscess. A combination of spread of the infection laterally from the abscess and compression lead to thrombosis of the IJV.

Patients will present with a history of bacterial sore throat followed by neck pain, stiffness and tenderness (may be mistaken for meningitis) and systemic involvement (fevers, rigors, etc). Septic pulmonary emboli may also occur.

# SULFONAMIDES

Sulfonamides are a class of antibiotic that work by inhibiting dihydropteroate synthetase

Examples
- co-trimoxazole
- trimethoprim

Adverse effects of co-trimoxazole include:
- hyperkalaemia
- headache
- rash (including Steven-Johnson Syndrome)

# TETRACYCLINES

Tetracyclines are a class of antibiotics which are commonly used in clinical practice.

Examples
- doxycycline
- tetracycline

Mechanism of action
- protein synthesis inhibitors
- binds to 30S subunit blocking binding of aminoacyl-tRNA

Mechanism of resistance
- increased efflux of the bacteria by plasmid-encoded transport pumps, ribosomal protection

Indications
- acne vulgaris
- Lyme disease
- Chlamydia
- Mycoplasma pneumoniae

Notable adverse effects
- discolouration of teeth: therefore should not be used in children < 12 years of age
- photosensitivity
- angioedema
- black hairy tongue

Tetracyclines should not be given to women who are pregnant or breastfeeding due to the risk of discolouration of the infant's teeth.

## TRIMETHOPRIM

Trimethoprim is an antibiotic, mainly used in the management of urinary tract infections.

Mechanism of action

- interferes with DNA synthesis by inhibiting dihydrofolate reductase
- may, therefore, interact with methotrexate, which also inhibits dihydrofolate reductase

Adverse effects

- myelosuppression
- transient rise in creatinine: trimethoprim competitively inhibits the tubular secretion of creatinine resulting in a temporary increase which reverses upon stopping the drug
- trimethoprim blocks the ENaC channel in the distal nephron, causing a hyperkalaemic distal RTA (type 4). It also inhibits creatinine secretion, often leading to an increase in creatinine by around 40 points (but not necessarily causing AKI)

Use in pregnancy
the BNF advises that there is a: 'Teratogenic risk in first trimester (folate antagonist). Manufacturers advise avoid during pregnancy.'

# MALARIA: INVESTIGATION

The gold standard for diagnosis of malaria remains the blood film. Rapid diagnostic tests (detecting plasmodial histidine-rich protein 2) are currently being trialled and have shown sensitivities from 77-99% and specificities from 83-98% for falciparum malaria

Blood film - if doubt about diagnosis should be repeated
- thick: more sensitive
- thin: determine species

Other tests
- thrombocythaemia is characteristic
- normochromic normocytic anaemia
- normal white cell count
- reticulocytosis

# MALARIA: NON-FALCIPARUM

The most common cause of non-falciparum malaria is Plasmodium vivax, with Plasmodium ovale and Plasmodium malariae accounting for the other cases. Plasmodium vivax is often found in Central America and the Indian Subcontinent whilst Plasmodium ovale typically comes from Africa.

Plasmodium knowlesi is another non-falciparum species which causes clinical pathology, found predominantly in South East Asia.

Features
- general features of malaria: fever, headache, splenomegaly
- Plasmodium vivax/ovale: cyclical fever every 48 hours. Plasmodium malariae: cyclical fever every 72 hours
- Plasmodium malariae: is associated with nephrotic syndrome.

Ovale and vivax malaria have a hypnozoite stage and may therefore relapse following treatment.

Treatment
- in areas which are known to be chloroquine-sensitive then WHO recommend either an artemisinin-based combination therapy (ACT) or chloroquine
- in areas which are known to be chloroquine-resistant an ACT should be used
- ACTs should be avoided in pregnant women
- patients with ovale or vivax malaria should be given primaquine following acute treatment with chloroquine to destroy liver hypnozoites and prevent relapse

# MALARIA: FALCIPARUM

Falciparum malaria is the commonest, and most severe, type of malaria.

Feature of severe malaria
- schizonts on a blood film
- parasitaemia > 2%
- hypoglycaemia
- acidosis
- temperature > 39 °C
- severe anaemia
- complications as below

Complications
- cerebral malaria: seizures, coma
- acute renal failure: blackwater fever, secondary to intravascular haemolysis, mechanism unknown
- acute respiratory distress syndrome (ARDS)
- hypoglycaemia
- disseminated intravascular coagulation (DIC)

Uncomplicated falciparum malaria
- strains resistant to chloroquine are prevalent in certain areas of Asia and Africa
- the 2010 WHO guidelines recommend artemisinin-based combination therapies (ACTs) as first-line therapy
- examples include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, dihydroartemisinin plus piperaquine

Severe falciparum malaria
- a parasite counts of more than 2% will usually need parenteral treatment irrespective of clinical state
- intravenous artesunate is now recommended by WHO in preference to intravenous quinine
- if parasite count > 10% then exchange transfusion should be considered
- shock may indicate coexistent bacterial septicaemia - malaria rarely causes haemodynamic collapse

# MALARIA: PROPHYLAXIS

There are around 1,500-2,000 cases each year of malaria in patients returning from endemic countries. The majority of these cases (around 75%) are caused by the potentially fatal Plasmodium falciparum protozoa. The majority of patients who develop malaria did not take prophylaxis. It should also be remembered that UK citizens who originate from malaria endemic areas quickly lose their innate immunity.

Up-to-date charts with recommended regimes for malarial zones should be consulted prior to prescribing

| Drug | Side-effects + notes | Time to begin before travel | Time to end after travel |
|---|---|---|---|
| Atovaquone + proguanil (Malarone) | GI upset | 1 - 2 days | 7 days |
| Chloroquine | Headache<br><br>Contraindicated in epilepsy<br>Taken weekly | 1 week | 4 weeks |
| Doxycycline | Photosensitivity<br>Oesophagitis | 1 - 2 days | 4 weeks |
| Mefloquine (Lariam) | Dizziness<br>Neuropsychiatric disturbance<br><br>Contraindicated in epilepsy<br>Taken weekly | 2 - 3 weeks | 4 weeks |
| Proguanil (Paludrine) | | 1 week | 4 weeks |
| Proguanil + chloroquine | See above | 1 week | 4 weeks |

Pregnant women should be advised to avoid travelling to regions where malaria is endemic. Diagnosis can also be difficult as parasites may not be detectable in the blood film due to placental sequestration. However, if travel cannot be avoided:

- chloroquine can be taken
- proguanil: folate supplementation (5mg od) should be given
- Malarone (atovaquone + proguanil): the BNF advises to avoid these drugs unless essential. If taken then folate supplementation should be given
- mefloquine: caution advised
- doxycycline is contraindicated

It is again advisable to avoid travel to malaria endemic regions with children if avoidable. However, if travel is essential then children should take malarial prophylaxis as they are more at risk of serious complications.

- diethyltoluamide (DEET) 20-50% has been shown to repel up to 100% of mosquitoes if used correctly. It can be used in children over 2 months of age*
- doxycycline is only licensed in the UK for children over the age of 12 years

*A BMJ review (BMJ 2015; 350:h99) suggest DEET could also be used in breastfeeding women and pregnant women in their 2nd or 3rd trimester

# PUBIC LICE

Pubic lice are also known as pediculosis pubis or phthiriasis pubis. It is most commonly a sexually transmitted infestation of the pubic hair by Phthirus pubis also known as the 'crab louse'. The incidence of the condition has been steadily decreasing over the past decade, which is believed to be in part due to changes in the population's grooming habits with regard to pubic hair.

Epidemiology

- The majority of pubic lice infestations are due to sexual contact and so can affect sexually active patients of any age, however are more common in men and in people aged 15-40 years of age.
- The range of estimated incidence has previously been as high as 4.0%, with average worldwide incidence of 2.0% however one study from the UK in 2014 showed an incidence of only 0.07%, which is likely linked to increased pubic hair removal rates.

Risk factors

- The primary risk factor for pubic lice is sexual contact, however Phthirus pubis does occasionally infest other sites of hair and so sexual contact is not always the cause. Incubation takes a minimum of 5 days, but a longer asymptomatic period is possible so time between sexual contact and symptoms may be many weeks.

Patients typically present with:

- Itching/pruritus- typically worse at night1: this may be localised to the pubic region or may affect any regions of body hair and rarely eyelashes and the head.
- Sometimes patient's may notice a 'black/rust-coloured powder' appearance in their underwear.

Signs:

- It may be possible to visualise individual lice, however microscopy may be required to see them.
- Excoriation marks due to repeated scratching due to pruritus.
- Blue macules (maculae ceruleae) may be visible: these are due to anticoagulant saliva injected by the lice during their feeding.

Investigations:

- The diagnosis is clinical.
- Microscopic/dermascopic evaluation of hair can help to evidence the presence of lice or eggs if they are not visible to the naked eye.3
- Patients presenting with pubic lice should be offered a full sexual health screen.

Management

- Clothing and bed linen should be decontaminated, either by washing at >50ºC or by placing in a sealed plastic bag for >7 days.
- Management of pubic lice involves application of either: malathion 0.5%, permethrin 1%, phenothrin 0.2% or carbaryl 0.5% All of these creams or lotions are applied to all body hair and left on the hair for the recommended 'treatment time' before being washed off.

- Treatment should be re-applied after 3-7 days: this is due to the presence of lice and eggs being at different stages of their life cycle.
- Mechanical removal should also be employed using nit-combs or similar techniques. However, shaving does not have a role in the management of pubic lice and should not be recommended.
- Re-examination should be performed approximately 1 week after treatment to ensure response to treatment.
- Contact tracing should also be performed and any sexual partners within the past 3 months should be examined and treated where appropriate.

## LYME DISEASE: FEATURES

Early features
- erythema migrans
- small papule often at site of the tick bite which develops into a larger annular lesion with central clearing, 'bulls-eye'.
- occurs in 70% of patients
- systemic symptoms: malaise, fever, arthralgia

Later features
- CVS: heart block, myocarditis
- neurological: cranial nerve palsies, meningitis
- polyarthritis

## LYME DISEASE

Lyme disease is caused by the spirochaete Borrelia burgdorferi and is spread by ticks.

Features
- early: erythema chronicum migrans ('bulls-eye') rash is seen in around 80%. Systemic features include fever, arthralgia
- cardiovascular: heart block, myocarditis
- neurological: facial nerve palsy, meningitis

Investigation
- NICE recommend that Lyme disease can be diagnosed clinically if erythema migrans is present
    - erythema migrans is therefore an indication to start antibiotics
- enzyme-linked immunosorbent assay (ELISA) antibodies to Borrelia burgdorferi are the first-line test

  - if negative and Lyme disease is still suspected in people tested within 4 weeks from symptom onset, repeat the ELISA 4-6 weeks after the first ELISA test. If still suspected in people who have had symptoms for 12 weeks or more then an immunoblot test should be done
  - if positive or equivocal then an immunoblot test for Lyme disease should be done

Management of asymptomatic tick bites
- tick bites can be a relatively common presentation to GP practices, and can cause significant anxiety
- NICE guidance does not recommend routine antibiotic treatment to patients who've suffered a tick bite

Management of suspected/confirmed Lyme disease
- doxycycline if early disease. Amoxicillin is an alternative if doxycycline is contraindicated (e.g. pregnancy)
  - people with erythema migrans should be commenced on antibiotic without the need for further tests
- ceftriaxone if disseminated disease
- Jarisch-Herxheimer reaction is sometimes seen after initiating therapy: fever, rash, tachycardia after first dose of antibiotic (more commonly seen in syphilis, another spirochaetal disease)

## TYPHUS

Overview
- rickettsial diseases
- transmitted between hosts by arthropods
- cause widespread vasculitis

Features
- fever, headache
- black eschar at site of original inoculation
- rash e.g. maculopapular or vasculitis
- complications: deranged clotting, renal failure, DIC

Rocky Mountain spotted fever
- caused by R rickettsii
- initially macular rash or hands and feet then spreads

Tick typhus
- caused by R conorii
- rash initially in axilla then spreads

# Q FEVER

Q fever is caused by Coxiella burnetii, a rickettsia. The source of infection is typically an abattoir, cattle/sheep or it may be inhaled from infected dust

Features
- typically prodrome: fever, malaise
- causes pyrexia of unknown origin
- transaminitis
- atypical pneumonia
- endocarditis (culture-negative)

Management
- doxycycline

# BRUCELLOSIS

Brucellosis is a zoonosis more common in the Middle East and in farmers. Four major species cause infection in humans: B melitensis (sheep), B abortus (cattle), B canis and B suis (pigs). Brucellosis has an incubation period 2 - 6 weeks

Features
- non-specific: fever, malaise
- hepatosplenomegaly
- sacroilitis: spinal tenderness may be seen
- complications: osteomyelitis, infective endocarditis, meningoencephalitis, orchitis
- leukopenia often seen

Diagnosis
- the Rose Bengal plate test can be used for screening but other tests are required to confirm the diagnosis
- Brucella serology is the best test for diagnosis
- blood and bone marrow cultures may be suitable in certain patients, but these tests are often negative

Management
- doxycycline and streptomycin

# ORF

Orf is generally a condition found in sheep and goats although it can be transmitted to humans. It is caused by the parapox virus.

In animals
- 'scabby' lesions around the mouth and nose

In humans
- generally affects the hands and arms
- initially small, raised, red-blue papules
- later may increase in size to 2-3 cm and become flat-topped and haemorrhagic

# TOXOPLASMOSIS

Toxoplasma gondii is a protozoa which infects the body via the GI tract, lung or broken skin. It's oocysts release trophozoites which migrate widely around the body including to the eye, brain and muscle. The usual animal reservoir is the cat, although other animals such as rats carry the disease.

Most infections are asymptomatic. Symptomatic patients usually have a self-limiting infection, often having clinical features resembling infectious mononucleosis (fever, malaise, lymphadenopathy). Other less common manifestations include meningioencephalitis and myocarditis.

Investigation
- antibody test
- Sabin-Feldman dye test

Treatment is usually reserved for those with severe infections or patients who are immunosuppressed
- pyrimethamine plus sulphadiazine for at least 6 weeks

Congenital toxoplasmosis is due to transplacental spread from the mother. It causes a variety of effects to the unborn child including microcephaly, hydrocephalus, cerebral calcification and choroidoretinitis.

# LEISHMANIASIS

Leishmaniasis is caused by the intracellular protozoa Leishmania, usually being spread by sand flies. Cutaneous, mucocutaneous leishmaniasis and visceral forms are seen

Cutaneous leishmaniasis
- caused by Leishmania tropica or Leishmania mexicana
- crusted lesion at site of bite
- may be underlying ulcer
- cutaneous leishmaniasis acquired in South or Central America merits treatment due to the risk of mucocutaneous leishmaniasis whereas disease acquired in Africa or India can be managed more conservatively

Mucocutaneous leishmaniasis
- caused by Leishmania braziliensis
- skin lesions may spread to involve mucosae of nose, pharynx etc

Visceral leishmaniasis (kala-azar)
- mostly caused by Leishmania donovani
- occurs in the Mediterranean, Asia, South America, Africa
- fever, sweats, rigors
- massive splenomegaly. hepatomegaly
- poor appetite*, weight loss
- grey skin - 'kala-azar' means black sickness
- pancytopaenia secondary to hypersplenism
- the gold standard for diagnosis is bone marrow or splenic aspirate

*occasionally patients may report increased appetite with paradoxical weight loss

# LEPTOSPIROSIS

Leptospirosis is caused by the spirochaete Leptospira interrogans (serogroup L. icterohaemorrhagiae), classically being spread by contact with infected rat urine.

Epidemiology
- leptospirosis is commonly seen in questions referring to sewage workers, farmers, vets or people who work in an abattoir
- however, on an international level, leptospirosis is far more common in the tropics so should be considered in the returning traveller

Weil's disease should always be considered in high-risk patients with hepatorenal failure

Features
- the early phase is due to bacteraemia and lasts around a week
    - may be mild or subclinical
    - fever
    - flu-like symptoms

  - subconjunctival suffusion (redness)/haemorrhage
- second immune phase may lead to more severe disease (Weil's disease)
  - acute kidney injury (seen in 50% of patients)
  - hepatitis: jaundice, hepatomegaly
  - aseptic meningitis

Investigation
- **serology**: antibodies to *Leptospira* develop after about 7 days
- PCR
- culture
  - growth may take several weeks so limits usefulness in diagnosis
  - blood and CSF samples are generally positive for the first 10 days
  - urine cultures become positive during the second week of illness

Management
- high-dose benzylpenicillin or doxycycline

## TRYPANOSOMIASIS

Two main form of this protozoal disease are recognised - African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas' disease).

Two forms of **African trypanosomiasis**, or **sleeping sickness**, are seen - *Trypanosoma gambiense* in West Africa and *Trypanosoma rhodesiense* in East Africa. Both types are spread by the tsetse fly. *Trypanosoma rhodesiense* tends to follow a more acute course. Clinical features include:
- Trypanosoma chancre - painless subcutaneous nodule at site of infection
- intermittent fever
- enlargement of posterior cervical lymph nodes
- later: central nervous system involvement e.g. somnolence, headaches, mood changes, meningoencephalitis

Management
- early disease: IV pentamidine or suramin
- later disease or central nervous system involvement: IV melarsoprol

**American trypanosomiasis**, or **Chagas' disease**, is caused by the protozoan *Trypanosoma cruzi*. The vast majority of patients (95%) are asymptomatic in the acute phase although a chagoma (an erythematous nodule at site of infection) and periorbital oedema are sometimes seen. Chronic Chagas' disease mainly affects the heart and gastrointestinal tract
myocarditis may lead to dilated cardiomyopathy (with apical atophy) and arrhythmias
gastrointestinal features includes megaoesophagus and megacolon causing dysphagia and constipation

Management
- treatment is most effective in the acute phase using azole or nitroderivatives such as benznidazole or nifurtimox
- chronic disease management involves treating the complications e.g., heart failure

# NEMATODES

Ancylostoma braziliense
- most common cause of cutaneous larva migrans
- common in Central and Southern America

Strongyloides stercoralis
- acquired percutaneously (e.g. walking barefoot)
- causes pruritus and larva currens - this has a similar appearance to cutaneous larva migrans but moves through the skin at a far greater rate
- abdo pain, diarrhoea, pneumonitis
- may cause Gram negative septicaemia due carrying of bacteria into bloodstream
- eosinophilia sometimes seen
- management: thiabendazole, albendazole. Ivermectin also used, particularly in chronic infections

Toxocara canis
- commonly acquired by ingesting eggs from soil contaminated by dog faeces
- commonest cause of visceral larva migrans
- other features: eye granulomas, liver/lung involvement

# STRONGYLOIDES STERCORALIS

Strongyloides stercoralis is a human parasitic nematode worm. The larvae are present in soil and gain access to the body by penetrating the skin. Infection with Strongyloides stercoralis causes strongyloidiasis.

Features
- diarrhoea
- abdominal pain/bloating
- papulovesicular lesions where the skin has been penetrated by infective larvae e.g. soles of feet and buttocks
- larva currens: pruritic, linear, urticarial rash
- if the larvae migrate to the lungs a pneumonitis similar to Loeffler's syndrome may be triggered

Treatment

- ivermectin and albendazole are used

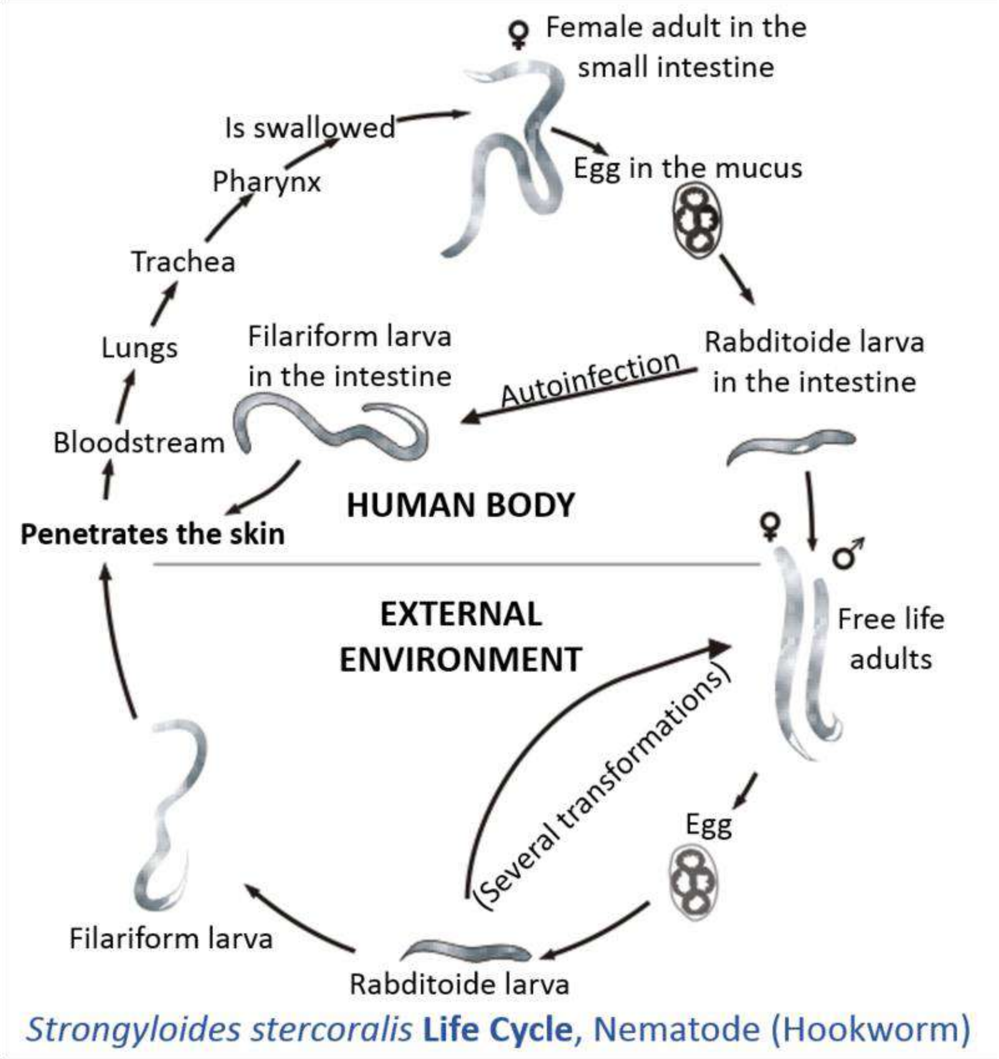

♀ Female adult in the small intestine
Is swallowed
Egg in the mucus
Pharynx
Trachea
Lungs
Filariform larva in the intestine
Autoinfection
Rabditoide larva in the intestine
Bloodstream
HUMAN BODY
Penetrates the skin
♀
♂
EXTERNAL ENVIRONMENT
Free life adults
(Several transformations)
Egg
Filariform larva
Rabditoide larva
Strongyloides stercoralis Life Cycle, Nematode (Hookworm)

Diagram showing the lifecycle of *Strongyloides stercoralis*

# SCHISTOSOMIASIS

Schistosomiasis, or bilharzia, is a parasitic flatworm infection. The three main species of schistosome are S. mansoni, S. japonicum and S. haematobium.

**Acute infections**

Acute symptoms typically only develop in people who travel to endemic areas, as they don't have any immunity to the worms.

Acute manifestations may include:

- swimmers' itch
- acute schistosomiasis syndrome (Katayama fever)

  - fever
  - urticaria/angioedema
  - arthralgia/myalgia
  - cough
  - diarrhoea
  - eosinophilia

**Chronic infections**

**Schistosoma haematobium**
These worms deposit egg clusters (pseudopapillomas) in the bladder, causing inflammation. The calcification seen on x-ray is actually calcification of the egg clusters, not the bladder itself.

Depending on the site of these pseudopapillomas in the bladder, they can cause an obstructive uropathy and kidney damage.

This typically presents as a 'swimmer's itch' in patients who have recently returned from Africa. Schistosoma haematobium is a risk factor for squamous cell bladder cancer.

Features
- frequency
- haematuria
- bladder calcification

Management
- single oral dose of praziquantel

**Schistosoma mansoni and Schistosoma japonicum**
These worms mature in the liver and then travel through the portal system to inhabit the distal colon. Their presence in the portal system can lead to progressive hepatomegaly and splenomegaly due to portal vein congestion.

These species can also lead to complications of liver cirrhosis, variceal disease and cor pulmonale.

**Schistosoma intercalatum and Schistosoma mekongi**
These are less prevalent than the other three forms, but are both attributed to intestinal schistosomiasis.

# TAPE WORMS

Tape worms are made up of repeated segments called proglottids. These are often present in faeces and are useful diagnostically

Cysticercosis

- caused by Taenia solium (from pork) and Taenia saginata (from beef)
- management: niclosamide

Hydatid disease

- caused by the dog tapeworm Echinococcus granulosus
- life-cycle involves dogs ingesting hydatid cysts from sheep liver
- often seen in farmers
- may cause liver cysts
- management: albendazole

# DNA VIRUSES

| Family | Structure | Envelope | Examples/importance |
|---|---|---|---|
| Herpesviruses | Double-stranded, linear | Enveloped | Herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus |
| Hepadnavirus | Double-stranded, circular | Enveloped | Hepatitis B virus |
| Adenovirus | Double-stranded, linear | Naked | Common cold, conjunctivitis |
| Parvovirus | **Single-stranded**, linear | Naked | Parvovirus B19 |
| Papillomavirus | Double-stranded, circular | Naked | HPV |
| Poxvirus | Double-stranded, linear | Enveloped | Smallpox, molluscum contagiosum |
| Polyomavirus | Double-stranded, circular | Naked | JC virus (progressive multifocal leukoencephalopathy) |

Parvovirus is the only DNA virus that is not double-stranded

HHAPPPPy! - Hepadna; Herpes; Adeno; Pox; Parvo; Papilloma; Polyoma

# RNA VIRUSES

| Family | Structure | Envelope | Capsid Symmetry | Examples |
|---|---|---|---|---|
| Reoviridae | **Double-stranded**, linear | Naked | Icosahedral | Reovirus, Rotavirus |
| Picornaviridae | Single-stranded +, linear | Naked | Icosahedral | Enterovirus, Rhinovirus, Poliovirus, Coxsackie |
| Caliciviridae | Single-stranded +, linear | Naked | Icosahedral | Norwalk virus |
| Togaviridae | Single-stranded +, linear | Enveloped | Icosahedral | Rubella virus |
| Arenaviridae | Single-stranded -, circular | Enveloped | Helical | Lymphocytic choriomeningitis virus |
| Flaviviridae | Single-stranded +, linear | Enveloped | Icosahedral | Dengue virus, Hepatitis C virus, Yellow fever virus |
| Orthomyxoviridae | Single-stranded -, linear | Enveloped | Helical | Influenzavirus A, Influenzavirus B, Influenzavirus C, |
| Paramyxoviridae | Single-stranded -, linear | Enveloped | Helical | Measles virus, Mumps virus, Respiratory syncytial virus |

| Family | Structure | Envelope | Capsid Symmetry | Examples |
|---|---|---|---|---|
| Bunyaviridae | Single-stranded -, circular | Enveloped | Helical | California encephalitis virus, Hantavirus |
| Rhabdoviridae | Single-stranded -, linear | Enveloped | Helical | Rabies virus |
| Filoviridae | Single-stranded -, linear | Enveloped | Helical | Ebola virus, Marburg virus |
| Coronaviridae | Single-stranded +, linear | Enveloped | Helical | Corona virus |
| Hepeviridae | Single-stranded +, linear | Naked | Icosahedral | Hepatitis E virus |

RNA viruses memory aids:

- Reoviridae are the only double-stranded RNA viruses
- 'CALL PICO and FLAVA. There's a RETRO TOGA party with lots of CORONAs'

# PARVOVIRUS B19

Parvovirus B19 is a DNA virus which causes a variety of clinical presentations. It was identified in the 1980's as the cause of erythema infectiosum

**Erythema infectiosum (also known as fifth disease or 'slapped-cheek syndrome')**

The illness may consist of a mild feverish illness which is hardly noticeable. However, in others there is a noticeable rash which appears after a few days. The rose-red rash makes the cheeks appear bright red, hence the name ‘slapped cheek syndrome’. The rash may spread to the rest of the body but unlike many other rashes, it only rarely involves the palms and soles.

The child begins to feel better as the rash appears and the rash usually peaks after a week and then fades. The rash is unusual in that for some months afterwards, a warm bath, sunlight, heat or fever will trigger a recurrence of the bright red cheeks and the rash itself. Most children recover and need no specific treatment. School exclusion is unnecessary as the child is not infectious once the rash emerges. In adults, the virus may cause acute arthritis.

Be aware that the virus can affect an unborn baby in the first 20 weeks of pregnancy. If a woman is exposed early in pregnancy (before 20 weeks) she should seek prompt advice from whoever is giving her antenatal care as maternal IgM and IgG will need to be checked. It is spread by the respiratory route and a person is infectious 3 to 5 days before the appearance of the rash. Children are no longer infectious once the rash appears and there is no specific treatment.

The child need not be excluded from school as they are no longer infectious by the time the rash occurs.

**Other presentations**

Other presentations include:

- asymptomatic
- pancytopaenia in immunosuppressed patients
- aplastic crises e.g. in sickle-cell disease (parvovirus B19 suppresses erythropoiesis for about a week so aplastic anaemia is rare unless there is a chronic haemolytic anaemia)

# HEPATITIS A

Hepatitis A is typically a benign, self-limiting disease, with a serious outcome being very rare.

Overview
- incubation period: 2-4 weeks
- RNA picornavirus
- transmission is by faecal-oral spread, often in institutions
- doesn't cause chronic disease

Features
- flu-like prodrome
- abdominal pain: typically right upper quadrant
- tender hepatomegaly
- jaundice
- cholestatic liver function tests

Complications
- complications are rare and there is no increased risk of hepatocellular cancer

Immunisation
- an effective vaccine is available
- after the initial dose a booster dose should be given 6-12 months later

Who should be vaccinated? (Based on the Green book guidelines)
- people travelling to or going to reside in areas of high or intermediate prevalence, if aged > 1 year old
- people with chronic liver disease
- patients with haemophilia
- men who have sex with men
- injecting drug users
- individuals at occupational risk: laboratory worker; staff of large residential institutions; sewage workers; people who work with primates

# HEPATITIS B

Hepatitis B is a double-stranded DNA hepadnavirus and is spread through exposure to infected blood or body fluids, including vertical transmission from mother to child. The incubation period is 6-20 weeks.

The features of hepatitis B include fever, jaundice and elevated liver transaminases.

Complications of hepatitis B infection

- chronic hepatitis (5-10%). 'Ground-glass' hepatocytes may be seen on light microscopy
- fulminant liver failure (1%)
- hepatocellular carcinoma
- glomerulonephritis
- polyarteritis nodosa
- cryoglobulinaemia

Immunisation against hepatitis B (please see the Greenbook link for more details)

- children born in the UK are now vaccinated as part of the routine immunisation schedule. This is given at 2, 3 and 4 months of age
- at risk groups who should be vaccinated include: healthcare workers, intravenous drug users, sex workers, close family contacts of an individual with hepatitis B, individuals receiving blood transfusions regularly, chronic kidney disease patients who may soon require renal replacement therapy, prisoners, chronic liver disease patients
- contains HBsAg adsorbed onto aluminium hydroxide adjuvant and is prepared from yeast cells using recombinant DNA technology
- around 10-15% of adults fail to respond or respond poorly to 3 doses of the vaccine. Risk factors include age over 40 years, obesity, smoking, alcohol excess and immunosuppression
- testing for anti-HBs is only recommended for those at risk of occupational exposure (i.e. Healthcare workers) and patients with chronic kidney disease. In these patients anti-HBs levels should be checked 1-4 months after primary immunisation
- the table below shows how to interpret anti-HBs levels:
-

| Anti-HBs level (mIU/ml) | Response |
|---|---|
| > 100 | Indicates adequate response, no further testing required. Should still receive booster at 5 years |
| 10 - 100 | Suboptimal response - one additional vaccine dose should be given. If immunocompetent no further testing is required |
| < 10 | Non-responder. Test for current or past infection. Give further vaccine course (i.e. 3 doses again) with testing following. If still fails to respond then HBIG would be required for protection if exposed to the virus |

Management of hepatitis B

- pegylated interferon-alpha used to be the only treatment available. It reduces viral replication in up to 30% of chronic carriers. A better response is predicted by being female, < 50 years old, low HBV DNA levels, non-Asian, HIV negative, high degree of inflammation on liver biopsy
- whilst NICE still advocate the use of pegylated interferon firstl-line other antiviral medications are increasingly used with an aim to suppress viral replication (not in a dissimilar way to treating HIV patients)

- examples include tenofovir, entecavir and telbivudine (a synthetic thymidine nucleoside analogue)

## HEPATITIS C

Hepatitis C is likely to become a significant public health problem in the UK in the next decade. It is thought around 200,000 people are chronically infected with the virus. At risk groups include intravenous drug users and patients who received a blood transfusion prior to 1991 (e.g. haemophiliacs).

Pathophysiology

- hepatitis C is a RNA flavivirus
- incubation period: 6-9 weeks

Transmission

- the risk of transmission during a needle stick injury is about 2%
- the vertical transmission rate from mother to child is about 6%. The risk is higher if there is coexistent HIV
- breastfeeding is not contraindicated in mothers with hepatitis C
- the risk of transmitting the virus during sexual intercourse is probably less than 5%
- there is no vaccine for hepatitis C

After exposure to the hepatitis C virus only around 30% of patients will develop features such as:

- a transient rise in serum aminotransferases / jaundice
- fatigue
- arthralgia

Investigations

- HCV RNA is the investigation of choice to diagnose acute infection
- whilst patients will eventually develop anti-HCV antibodies it should be remembered that patients who spontaneously clear the virus will continue to have anti-HCV antibodies

Outcome

- around 15-45% of patients will clear the virus after an acute infection (depending on their age and underlying health) and hence the majority (55-85%) will develop chronic hepatitis C

**Chronic hepatitis C**

Chronic hepatitis C may be defined as the persistence of HCV RNA in the blood for 6 months.

Potential complications of chronic hepatitis C

- rheumatological problems: arthralgia, arthritis
- eye problems: Sjogren's syndrome

- cirrhosis (5-20% of those with chronic disease)
- hepatocellular cancer
- cryoglobulinaemia: typically type II (mixed monoclonal and polyclonal)
- porphyria cutanea tarda (PCT): it is increasingly recognised that PCT may develop in patients with hepatitis C, especially if there are other factors such as alcohol abuse
- membranoproliferative glomerulonephritis

Management of chronic infection

- treatment depends on the viral genotype - this should be tested prior to treatment
- the management of hepatitis C has advanced rapidly in recent years resulting in clearance rates of around 95%. Interferon based treatments are no longer recommended
- the aim of treatment is sustained virological response (SVR), defined as undetectable serum HCV RNA six months after the end of therapy
- currently a combination of protease inhibitors (e.g. daclatasvir + sofosbuvir or sofosbuvir + simeprevir) with or without ribavirin are used

Complications of treatment

- ribavirin - side-effects: haemolytic anaemia, cough. Women should not become pregnant within 6 months of stopping ribavirin as it is teratogenic
- interferon alpha - side-effects: flu-like symptoms, depression, fatigue, leukopenia, thrombocytopenia

# HEPATITIS E

Overview

- RNA hepevirus
- spread by the faecal-oral route
- incubation period: 3-8 weeks
- common in Central and South-East Asia, North and West Africa, and in Mexico
- causes a similar disease to hepatitis A, but carries a significant mortality (about 20%) during pregnancy
- does not cause chronic disease or an increased risk of hepatocellular cancer
- a vaccine is currently in development*, but is not yet in widespread use

*New England Journal of Medicine 356:895, 2007

# RABIES

Rabies is a viral disease that causes an acute encephalitis. The rabies virus is classed as a RNA rhabdovirus (specifically a lyssavirus) and has a bullet-shaped capsid. The vast majority of cases are caused by dog bites but it may also be transmitted by bat, raccoon and skunk bites. Following a bite the virus travels up the nerve axons towards the central nervous system in a retrograde fashion.

Rabies is estimated to still kill around 25,000-50,000 people across the world each year. The vast majority of the disease burden falls on people in poor rural areas of Africa and Asia. Children are particularly at risk.

Features
- prodrome: headache, fever, agitation
- hydrophobia: water-provoking muscle spasms
- hypersalivation
- Negri bodies: cytoplasmic inclusion bodies found in infected neurons

There is now considered to be 'no risk' of developing rabies following an animal bite in the UK and the majority of developed countries. Following an animal bite in at-risk countries:
- the wound should be washed
- if an individual is already immunised then 2 further doses of vaccine should be given
- if not previously immunised then human rabies immunoglobulin (HRIG) should be given along with a full course of vaccination. If possible, the dose should be administered locally around the wound

If untreated the disease is nearly always fatal.

# JAPANESE ENCEPHALITIS

Japanese encephalitis is the most common cause of viral encephalitis in South East Asia, China the Western Pacific and India, with approx. 50,000 cases annually. It is a flavivirus transmitted by culex mosquitos which breeds in rice paddy fields. The reservoir hosts are aquatic birds, but pigs are an amplification host and therefore close domestic contact with pigs is a risk factor.

The majority of infection is asymptomatic.

Clinical features are headache, fever, seizures and confusion. Parkinsonian features indicate basal ganglia involvement. It can also present with acute flaccid paralysis.

Diagnosis is by serology or PCR. Management is supportive.

Prevention is a vaccine and there are a variety of different types.

## HIV: TESTING

HIV antibody test

- most common and accurate test
- usually consists of both a screening ELISA (Enzyme Linked Immuno-Sorbent Assay) test and a confirmatory Western Blot Assay
- most people develop antibodies to HIV at 4-6 weeks but 99% do by 3 months

p24 antigen test

- usually positive from about 1 week to 3 - 4 weeks after infection with HIV
- sometimes used as an additional screening test in blood banks

## HIV: SEROCONVERSION

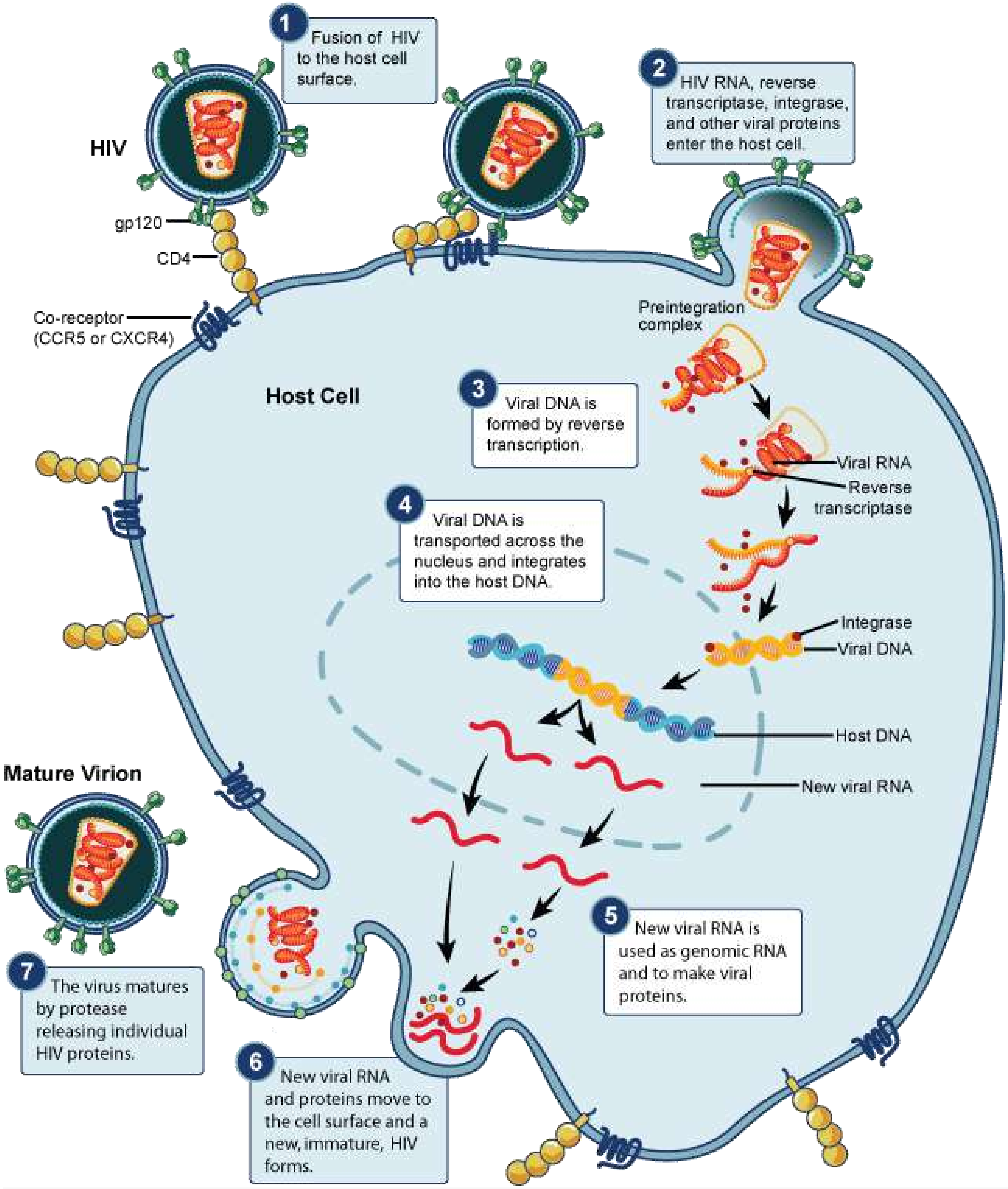
HIV seroconversion is symptomatic in 60-80% of patients and typically presents as a glandular fever type illness. Increased symptomatic severity is associated with poorer long term prognosis. It typically occurs 3-12 weeks after infection

Features

- sore throat
- lymphadenopathy
- malaise, myalgia, arthralgia
- diarrhoea
- maculopapular rash
- mouth ulcers
- rarely meningoencephalitis

Diagnosis

- antibodies to HIV may not be present
- HIV PCR and p24 antigen tests can confirm diagnosis


1
Fusion of HIV to the host cell surface.
HIV
gp120
CD4
Co-receptor (CCR5 or CXCR4)
2
HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell.
Preintegration complex
Host Cell
3
Viral DNA is formed by reverse transcription.
Viral RNA
Reverse transcriptase
4
Viral DNA is transported across the nucleus and integrates into the host DNA.
Integrase
Viral DNA
Host DNA
New viral RNA
Mature Virion
5
New viral RNA is used as genomic RNA and to make viral proteins.
7
The virus matures by protease releasing individual HIV proteins.
6
New viral RNA and proteins move to the cell surface and a new, immature, HIV forms.

An illustration model of the HIV Replication Cycle. Each step of the cycle is numbered and concisely described. Credit: NIAID

## HIV: MANAGEMENT

Antiretroviral therapy (ART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging

Following the 2015 BHIVA guidelines it is now recommended that patients start ART as soon as they have been diagnosed with HIV, rather than waiting until a particular CD4 count, as was previously advocated.

Entry inhibitors

- maraviroc (binds to CCR5, preventing an interaction with gp41), enfuvirtide (binds to gp41, also known as a 'fusion inhibitor')
- prevent HIV-1 from entering and infecting immune cells

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), abacavir, emtricitabine, didanosine, lamivudine, stavudine, zalcitabine, tenofovir
- general NRTI side-effects: peripheral neuropathy
- tenofovir: used in BHIVAs two recommended regime NRTI. Adverse effects include renal impairment and ostesoporosis
- zidovudine: anaemia, myopathy, black nails
- didanosine: pancreatitis

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine induces), rashes

Protease inhibitors (PI)

- examples: indinavir, nelfinavir, ritonavir, saquinavir
- side-effects: diabetes, hyperlipidaemia, buffalo hump, central obesity, P450 enzyme inhibition
- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

Integrase inhibitors

- examples: raltegravir, elvitegravir, dolutegravir

# IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Immune reconstitution inflammatory syndrome is a condition generally associated with HIV/immunosuppression, in which the immune system begins to recover, but then responds to a previously acquired opportunistic infection with an overwhelming inflammatory response that paradoxically makes the symptoms of infection worse.

# HIV: OPPORTUNISTIC INFECTIONS AND OTHER DISORDERS

The table below shows the infections and other disorders that may be encountered by patients with HIV according to the CD4 count.

**CD4 count 200 - 500 cells/mm³**

| Disorder | Notes |
|---|---|
| Oral thrush | Secondary to *Candida albicans* |
| Shingles | Secondary to herpes zoster |
| Hairy leukoplakia | Secondary to EBV |
| Kaposi sarcoma | Secondary to HHV-8 |

**CD4 count 100 - 200 cells/mm³**

| Disorder | Notes |
|---|---|
| Cryptosporidiosis | Whilst patients with a CD4 count of 200-500 may develop cryptosporidiosis the disease is usually self-limiting and similar to that in immunocompetent hosts |
| Cerebral toxoplasmosis | |
| Progressive multifocal leukoencephalopathy | Secondary to the JC virus |
| Pneumocystis jirovecii pneumonia | |
| HIV dementia | |

**CD4 count 50 - 100 cells/mm³**

| Disorder | Notes |
|---|---|
| Aspergillosis | Secondary to *Aspergillus fumigatus* |
| Oesophageal candidiasis | Secondary to *Candida albicans* |
| Cryptococcal meningitis | |
| Primary CNS lymphoma | Secondary to EBV |

**CD4 count < 50 cells/mm³**

| Disorder | Notes |
|---|---|
| Cytomegalovirus retinitis | Affects around 30-40% of patients with CD4 < 50 cells/mm³ |

| Disorder | Notes |
|---|---|
| Mycobacterium avium-intracellulare infection | |

# HIV: PNEUMOCYSTIS JIROVECI PNEUMONIA

Whilst the organism Pneumocystis carinii is now referred to as Pneumocystis jiroveci, the term Pneumocystis carinii pneumonia (PCP) is still in common use

- Pneumocystis jiroveci is an unicellular eukaryote, generally classified as a fungus but some authorities consider it a protozoa
- PCP is the most common opportunistic infection in AIDS
- all patients with a CD4 count < $200/mm^3$ should receive PCP prophylaxis

Features

- dyspnoea
- dry cough
- fever
- very few chest signs

Pneumothorax is a common complication of PCP.

Extrapulmonary manifestations are rare (1-2% of cases), may cause

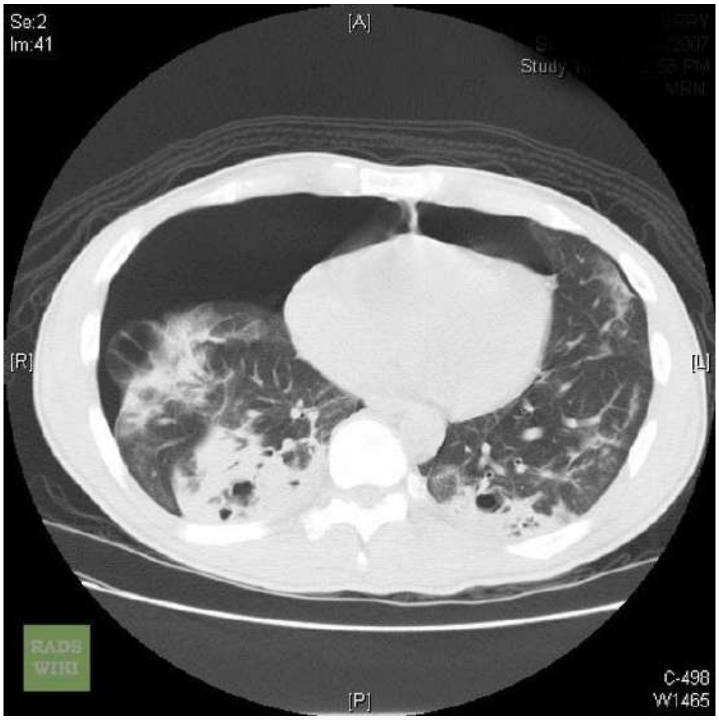
- hepatosplenomegaly
- lymphadenopathy
- choroid lesions

Investigation

- CXR: typically shows bilateral interstitial pulmonary infiltrates but can present with other x-ray findings e.g. lobar consolidation. May be normal
- exercise-induced desaturation
- sputum often fails to show PCP, bronchoalveolar lavage (BAL) often needed to demonstrate PCP (silver stain shows characteristic cysts)

Management

- co-trimoxazole
- IV pentamidine in severe cases
- aerosolized pentamidine is an alternative treatment for Pneumocystis jiroveci pneumonia but is less effective with a risk of pneumothorax
- steroids if hypoxic (if pO2 < 9.3kPa then steroids reduce risk of respiratory failure by 50% and death by a third)



CT scan showing a large pneumothorax developing in a patient with *Pneumocystis jiroveci* pneumonia

## HIV: DIARRHOEA

Diarrhoea is common in patients with HIV. This may be due to the effects of the virus itself (HIV enteritis) or opportunistic infections

Possible causes

- Cryptosporidium + other protozoa (most common)
- Cytomegalovirus
- *Mycobacterium avium intracellulare*
- Giardia

Cryptosporidium is the most common infective cause of diarrhoea in HIV patients. It is an intracellular protozoa and has an incubation period of 7 days. Presentation is very variable, ranging from mild to severe diarrhoea. A modified Ziehl-Neelsen stain (acid-fast stain) of the stool may reveal the characteristic red cysts of Cryptosporidium. Treatment is difficult, with the mainstay of management being supportive therapy*

*Mycobacterium avium intracellulare* is an atypical mycobacteria seen with the CD4 count is below 50. Typical features include fever, sweats, abdominal pain and diarrhoea. There may be hepatomegaly and deranged LFTs. Diagnosis is made by blood cultures and bone marrow examination. Management is with rifabutin, ethambutol and clarithromycin

*nitazoxanide is licensed in the US for immunocompetent patients

# HIV: MYCOBACTERIUM AVIUM COMPLEX

Mycobacterium avium complex (MAC) is an atypical mycobacterial infection seen in HIV patients. It is caused by both Mycobacterium avium and Mycobacterium intracellulare, and is often referred to as Mycobacterium avium-intracellulare (MAI). Over 95% of MAC infections in patients with HIV are caused by Mycobacterium avium. MAC is generally seen when the CD4 count is less than 50 cells/mm$^3$

Features
- fever, sweats
- abdominal: pain, diarrhoea
- lung: dyspnoea, cough
- anaemia
- lymphadenopathy
- hepatomegaly/deranged LFTs

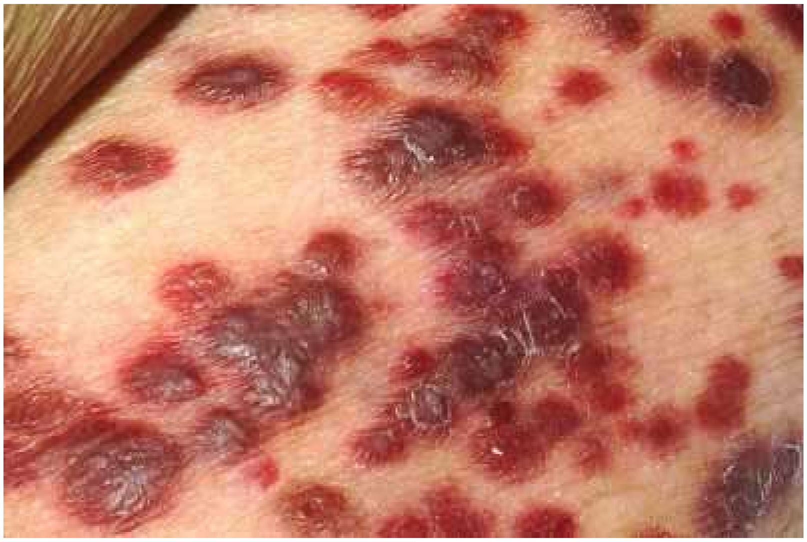
Diagnosis
- blood cultures
- bone marrow aspirate

Prophylaxis
- clarithromycin or azithromycin when CD4 is less than 100 cells/mm$^3$

Management
- rifampicin + ethambutol + clarithromycin

# HIV: KAPOSI'S SARCOMA

- Kaposi's sarcoma
- caused by HHV-8 (human herpes virus 8)
- presents as purple papules or plaques on the skin or mucosa (e.g. gastrointestinal and respiratory tract)
- skin lesions may later ulcerate
- respiratory involvement may cause massive haemoptysis and pleural effusion
- radiotherapy + resection



Kaposi's sarcoma in a patient with HIV

## HIV: CYTOMEGALOVIRUS RETINITIS

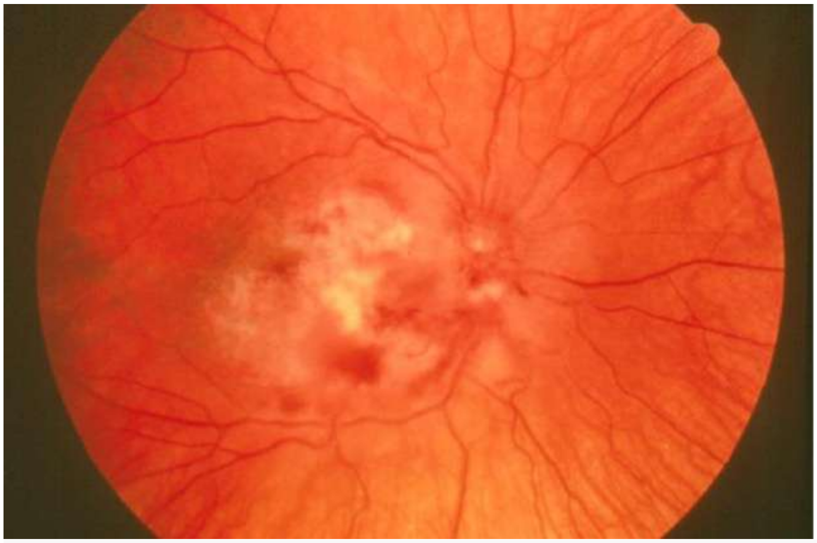
Cytomegalovirus (CMV) retinitis is common, affecting 30-40% of patients who have a CD4 count < 50. Diagnosis is clinical as there are no diagnostic tests

Features

- visual impairment - 'blurred vision' etc

Fundoscopy

- characteristic appearance showing retinal haemorrhages and necrosis
- often called 'pizza' retina



Fundus photograph showing CMV retinitis. Credit: National Eye Institute, National Institutes of Health

Management

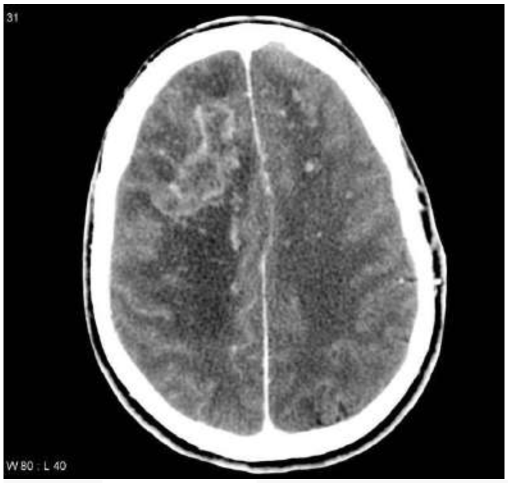
- IV ganciclovir
- treatment used to be life-long but new evidence suggests that it may be discontinued once CD4 > 150 after HAART
- alternative: IV foscarnet or cidofovir

# HIV: NEUROCOMPLICATIONS

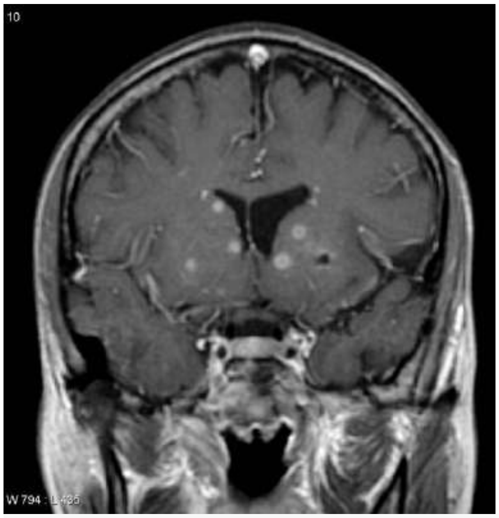
**Focal neurological lesions**

Toxoplasmosis

- accounts for around 50% of cerebral lesions in patients with HIV
- constitutional symptoms, headache, confusion, drowsiness
- CT: usually single or multiple ring enhancing lesions, mass effect may be seen
- management: sulfadiazine and pyrimethamine



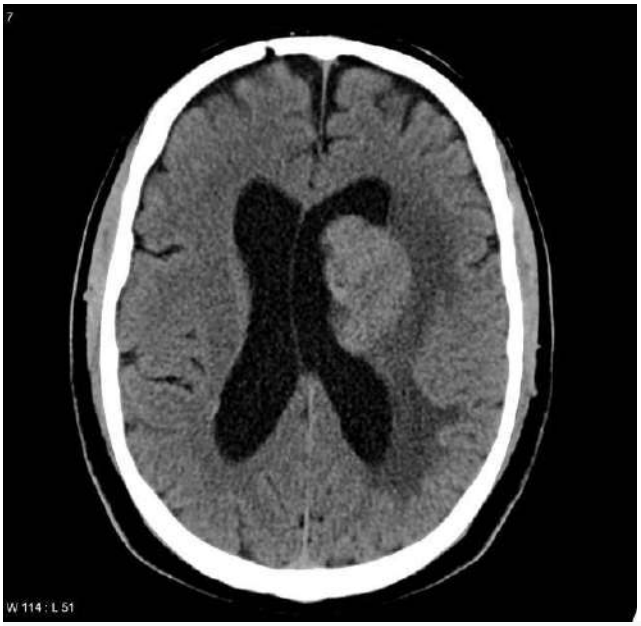
Cerebral toxoplasmosis: CT scan with contrast showing multiple ring enhancing lesions



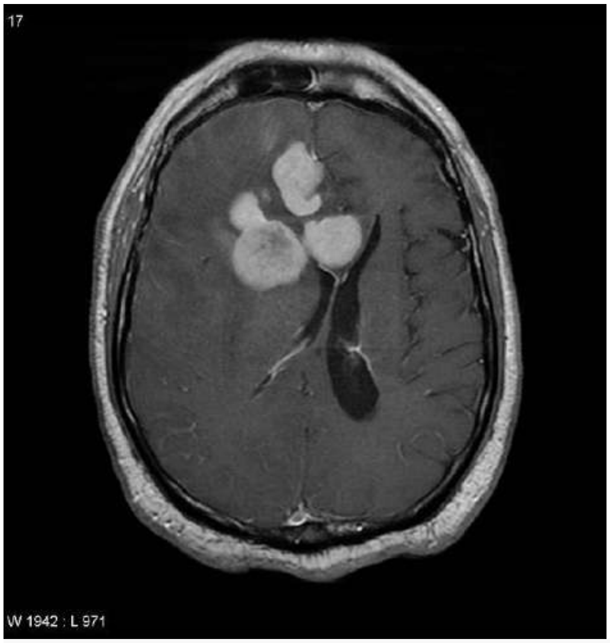
Cerebral toxoplasmosis: MRI (T1 C+) demonstrates multiple small peripherally enhancing nodules located predominantly in the basal ganglia as well as the central portions of the cerebellar hemispheres. Only a small amount of surrounding oedema is present.

Primary CNS lymphoma

- accounts for around 30% of cerebral lesions
- associated with the Epstein-Barr virus
- CT: single or multiple homogenous enhancing lesions
- treatment generally involves steroids (may significantly reduce tumour size), chemotherapy (e.g. methotrexate) + with or without whole brain irradiation. Surgical may be considered for lower grade tumours



Primary CNS lymphoma: Non-contrast CT demonstrates a hyper-attenuating mass adjacent to the left lateral ventricle, with no calcification or haemorrhage.



Primary CNS lymphoma: MRI (T1 C+) demonstrates a large multilobulated mass in the right frontal lobe. It homogeneously enhances and extends to involve the caudate and the periventricular area. There is significant mass effect.

| Toxoplasmosis | Lymphoma |
|---|---|
| Multiple lesions<br>Ring or nodular enhancement<br>Thallium SPECT negative | Single lesion<br>Solid (homogenous) enhancement<br>Thallium SPECT positive |

Tuberculosis

- much less common than toxoplasmosis or primary CNS lymphoma
- CT: single enhancing lesion

**Generalised neurological disease**

Encephalitis

- may be due to CMV or HIV itself
- HSV encephalitis but is relatively rare in the context of HIV
- CT: oedematous brain

*Cryptococcus*

- most common fungal infection of CNS
- headache, fever, malaise, nausea/vomiting, seizures, focal neurological deficit
- CSF: high opening pressure, India ink test positive
- CT: meningeal enhancement, cerebral oedema
- meningitis is typical presentation but may occasionally cause a space occupying lesion

Progressive multifocal leukoencephalopathy (PML)

- widespread demyelination
- due to infection of oligodendrocytes by JC virus (a polyoma DNA virus)
- symptoms, subacute onset : behavioural changes, speech, motor, visual impairment
- CT: single or multiple lesions, no mass effect, don't usually enhance. MRI is better - high-signal demyelinating white matter lesions are seen

AIDS dementia complex

- caused by HIV virus itself
- symptoms: behavioural changes, motor impairment
- CT: cortical and subcortical atrophy

# HIV AND PREGNANCY

With the increased incidence of HIV infection amongst the heterosexual population there are an increasing number of HIV positive women giving birth in the UK. In London the incidence may be as high as 0.4% of pregnant women. The aim of treating HIV positive women during pregnancy is to minimise harm to both the mother and fetus, and to reduce the chance of vertical transmission.

Guidelines regularly change on this subject and most recent guidelines can be found using the links provided.

Factors which reduce vertical transmission (from 25-30% to 2%)
- maternal antiretroviral therapy
- mode of delivery (caesarean section)
- neonatal antiretroviral therapy
- infant feeding (bottle feeding)

Screening
- NICE guidelines recommend offering HIV screening to all pregnant women

Antiretroviral therapy
- all pregnant women should be offered antiretroviral therapy regardless of whether they were taking it previously

Mode of delivery
- vaginal delivery is recommended if viral load is less than 50 copies/ml at 36 weeks, otherwise caesarian section is recommended
- a zidovudine infusion should be started four hours before beginning the caesarean section

Neonatal antiretroviral therapy
- zidovudine is usually administered orally to the neonate if maternal viral load is <50 copies/ml. Otherwise triple ART should be used. Therapy should be continued for 4-6 weeks.

Infant feeding
- in the UK all women should be advised not to breast feed

# EPSTEIN-BARR VIRUS: ASSOCIATED CONDITIONS

Malignancies associated with EBV infection
- Burkitt's lymphoma*
- Hodgkin's lymphoma
- nasopharyngeal carcinoma
- HIV-associated central nervous system lymphomas

The non-malignant condition hairy leukoplakia is also associated with EBV infection.

*EBV is currently thought to be associated with both African and sporadic Burkitt's

# CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is one of the herpes viruses. It is thought that around 50% of people have been exposed to the CMV virus although it only usually causes disease in the immunocompromised, for example people with HIV or those on immunosuppressants following organ transplantation.

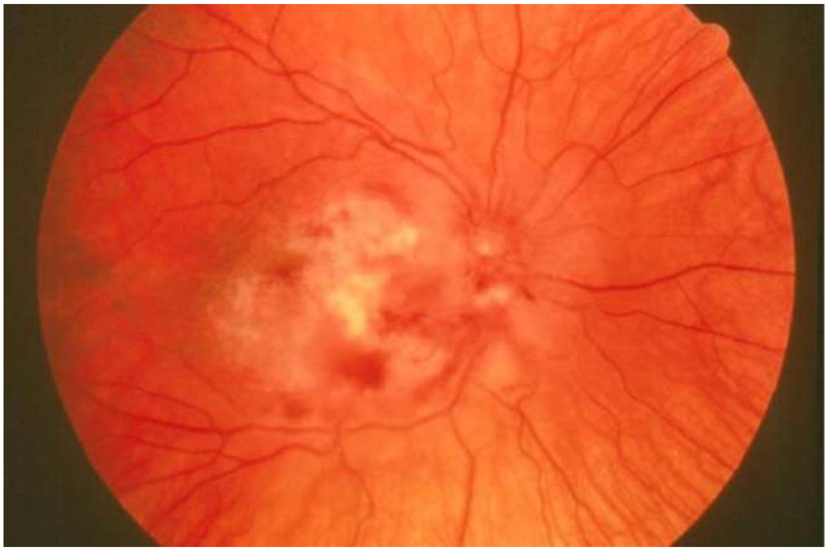
Pathophysiology
- infected cells have a 'Owl's eye' appearance due to intranuclear inclusion bodies

**Patterns of disease**

Congenital CMV infection
- features include growth retardation, pinpoint petechial 'blueberry muffin' skin lesions, microcephaly, sensorineural deafness, encephalitiis (seizures) and hepatosplenomegaly

CMV mononucleosis
- infectious mononucelosis-like illness
- may develop in immunocompetent individuals

CMV retinitis
- common in HIV patients with a low CD4 count (< 50)
- presents with visual impairment e.g. 'blurred vision'. Fundoscopy shows retinal haemorrhages and necrosis, often called 'pizza' retina
- IV ganciclovir is the treatment of choice



Fundus photograph showing CMV retinitis. Credit: National Eye Institute, National Institutes of Health

CMV encephalopathy

- seen in patients with HIV who have low CD4 counts

CMV pneumonitis

CMV colitis

## CHIKUNGUNYA

Alphavirus disease caused by infected mosquitoes. Areas affected are Africa, Asia and Indian subcontinent but in recent years there has been seen in a few cases in Southern Europe. Tanzania had the first reported case.

Symptoms: Prominent symptoms are severe joint pain and abrupt onset of high fever. Other symptoms include general flu-like illness of muscle ache, headache, and fatigue. The disease shares its symptoms with dengue but tends to have more joint pain which can be debilitating. A rash may develop as with other viral illness and swelling of the joints in not uncommon.

Treatment: Relief of symptoms. No specific treatment.

# VIRAL HAEMORRHAGIC FEVERS

Viral haemorrhagic fevers (VHFs) are a group of viral infections that result in presentations ranging from a flu-like illness to multisystem failure.

Examples of viral haemorrhagic fever (VHF) include:
- Flaviviridae: dengue, yellow fever
- Arenaviridae: Lassa fever
- Filoviridae: Ebola virus, Marburg virus
- Bunyaviridae: Hantaviruses, Crimean-Congo haemorrhagic fever, Rift Valley fever

Features
- flu-like symptoms
- abdominal pain
- haemorrhage
  - petechiae, bruising
  - bloody diarrhoea, haematemesis, haemoptysis
  - disseminated intravascular coagulation
- multiorgan failure

Prevention
- a yellow fever vaccine is available
- a dengue and Ebola vaccine have been developed but are now widely used at the current time
- no vaccines are available for the other VHFs

Management
- treatment is generally supportive
- ribavirin is used to treat Lassa fever

The more common VHFs such as dengue, Ebola and yellow fever are covered in more detail elsewhere in the notes.

**Lassa fever**
Lassa fever is contracted by contact with the excreta of infected African rats (Mastomys rodent) or by person-to-person spread.

**Marburg virus**
Causes a VHF very similar to Ebola.

Risk factors for transmissions include caves/bats and primates.

# YELLOW FEVER

Type of viral haemorrhagic fever (also dengue fever, Lassa fever, Ebola).

Basics
- zoonotic infection: spread by Aedes mosquitos
- incubation period = 2 - 14 days

Features
- may cause mild flu-like illness lasting less than one week
- classic description involves sudden onset of high fever, rigors, nausea & vomiting. Bradycardia may develop. A brief remission is followed by jaundice, haematemesis, oliguria
- if severe jaundice, haematemesis may occur
- Councilman bodies (inclusion bodies) may be seen in the hepatocytes

# DENGUE FEVER

Dengue fever is a viral infection which can progress to viral haemorrhagic fever (also yellow fever, Lassa fever, Ebola)

Basics
- transmitted by the Aedes aegypti mosquito
- incubation period of 7 days
- a form of disseminated intravascular coagulation (DIC) known as dengue haemorrhagic fever (DHF) may develop. Around 20-30% of these patients go on to develop dengue shock syndrome (DSS)

Features
- causes headache (often retro-orbital)
- fever
- myalgia
- pleuritic pain
- facial flushing (dengue)
- maculopapular rash

Treatment
- entirely symptomatic e.g. fluid resuscitation, blood transfusion etc
- no antivirals are currently available

# H1N1

The H1N1 virus is a subtype of the influenza A virus and the most common cause of flu in humans. The 2009 pandemic was caused by a new strain of the H1N1 virus.

The following groups are particularly at risk:
- patients with chronic illnesses and those on immunosuppressants
- pregnant women
- young children under 5 years old

**Features**
The majority of symptoms are typical of those seen in a flu-like illness:
- fever greater than 38ºC
- myalgia
- lethargy
- headache
- rhinitis
- sore throat
- cough
- diarrhoea and vomiting

A minority of patients may go on to develop an acute respiratory distress syndrome which may require ventilatory support.

**Treatment**
There are two main treatments currently available:

Oseltamivir (Tamiflu)
- oral medication
- a neuraminidase inhibitor which prevents new viral particles from being released by infected cells
- common side-effects include nausea, vomiting, diarrhoea and headaches

Zanamivir (Relenza)
- inhaled medication*
- also a neuraminidase inhibitor
- may induce bronchospasm in asthmatics

*intravenous preparations are available for patients who are acutely unwell

# ZIKA VIRUS

Zika is a mosquito-borne infection caused by Zika virus, a member of the genus flavivirus and family Flaviviridae. It was first isolated from a monkey in the Zika forest in Uganda in 1947.

Transmission is usually via the bite of an infected Aedes mosquito, although a small number of cases of sexual transmission have been reported. There is increasing evidence of transmission via the placenta from mother to fetus.

The majority of people infected with Zika virus have no symptoms. For those with symptoms, Zika virus tends to cause a mild, short-lived (2 to 7 days) febrile disease. Signs and symptoms suggestive of Zika virus infection may include a combination of the following:

- fever
- rash
- arthralgia/arthritis
- conjunctivitis
- myalgia
- headache
- retro-orbital pain
- pruritus

Serious complications in adults are not common, although the virus has been associated with Guillain-Barre syndrome. Scientific consensus however has linked Zika with microcephaly and other congenital abnormalities, which has led the World Health Organisation (WHO) to declare a Public Health Emergency of International Concern (PHEIC).

# SPLENECTOMY

Following a splenectomy patients are particularly at risk from pneumococcus, Haemophilus, meningococcus and Capnocytophaga canimorsus* infections

Vaccination
- if elective, should be done 2 weeks prior to operation
- Hib, meningitis A & C
- annual influenza vaccination
- pneumococcal vaccine every 5 years

Antibiotic prophylaxis
- penicillin V: unfortunately clear guidelines do not exist of how long antibiotic prophylaxis should be continued. It is generally accepted though that penicillin should be continued for at least 2 years and at least until the patient is 16 years of age, although the majority of patients are usually put on antibiotic prophylaxis for life

**Surgical aspects**
Indications
- Trauma: 1/4 are iatrogenic
- Spontaneous rupture: EBV
- Hypersplenism: hereditary spherocytosis or elliptocytosis etc
- Malignancy: lymphoma or leukaemia
- Splenic cysts, hydatid cysts, splenic abscesses

Elective splenectomy
- Elective splenectomy is a very different operation from that performed in the emergency setting. The spleen is often large (sometimes massive)
- Most cases can be performed laparoscopically. The spleen will often be macerated inside a specimen bag to facilitate extraction.

Complications
- Haemorrhage (may be early and either from short gastrics or splenic hilar vessels
- Pancreatic fistula (from iatrogenic damage to pancreatic tail)
- Thrombocytosis: prophylactic aspirin
- Encapsulated bacteria infection e.g. Strep. pneumoniae, Haemophilus influenzae and Neisseria meningitidis

Post-splenectomy changes
- Platelets will rise first (therefore in ITP should be given after splenic artery clamped)
- Blood film will change over following weeks, Howell-Jolly bodies will appear
- Other blood film changes include target cells and Pappenheimer bodies

- Increased risk of post-splenectomy sepsis, therefore prophylactic antibiotics and pneumococcal vaccine should be given.

Post-splenectomy sepsis
- Typically occurs with encapsulated organisms
- Opsonisation occurs but then not recognised

*usually from dog bites

# VACCINATIONS

It is important to be aware of vaccines which are of the live-attenuated type as these may pose a risk to immunocompromised patients. The main types of vaccine are as follows:

Live attenuated
- BCG
- measles, mumps, rubella (MMR)
- influenza (intranasal)
- oral rotavirus
- oral polio
- yellow fever
- oral typhoid

Inactivated preparations
- rabies
- hepatitis A
- influenza (intramuscular)

Toxoid (inactivated toxin)
- tetanus
- diphtheria
- pertussis

Subunit and conjugate vaccines are often grouped together. Subunit means that only part of the pathogen is used to generate an immunogenic response. A conjugate vaccine is a particular type that links the poorly immunogenic bacterial polysaccharide outer coats to proteins to make them more immunogenic
- pneumococcus (conjugate)
- haemophilus (conjugate)
- meningococcus (conjugate)
- hepatitis B
- human papillomavirus

,

Notes
- influenza: different types are available, including whole inactivated virus, split virion (virus particles disrupted by detergent treatment) and sub-unit (mainly haemagglutinin and neuraminidase)
- cholera: contains inactivated Inaba and Ogawa strains of Vibrio cholerae together with recombinant B-subunit of the cholera toxin
- hepatitis B: contains HBsAg adsorbed onto aluminium hydroxide adjuvant and is prepared from yeast cells using recombinant DNA technology

# BCG VACCINE

The Bacille Calmette-Guérin (BCG) vaccine offers limited protection against tuberculosis (TB). In the UK it is given to high-risk infants. Until 2005 it was also routinely given to children at the age of 13 years.

The Greenbook currently advises that the vaccine is administered to the following groups (below is summary, please see the link for more details):

- all infants (aged 0 to 12 months) living in areas of the UK where the annual incidence of TB is 40/100,000 or greater
- all infants (aged 0 to 12 months) with a parent or grandparent who was born in a country where the annual incidence of TB is 40/100,000 or greater. The same applies to older children but if they are 6 years old or older they require a tuberculin skin test first
- previously unvaccinated tuberculin-negative contacts of cases of respiratory TB
- previously unvaccinated, tuberculin-negative new entrants under 16 years of age who were born in or who have lived for a prolonged period (at least three months) in a country with an annual TB incidence of 40/100,000 or greater
- healthcare workers
- prison staff
- staff of care home for the elderly
- those who work with homeless people

The vaccine contains live attenuated Mycobacterium bovis. It also offers limited protection against leprosy.

Administration

- any person being considered for the BCG vaccine must first be given a tuberculin skin test. The only exceptions are children < 6 years old who have had no contact with tuberculosis
- given intradermally, normally to the lateral aspect of the left upper arm
- BCG can be given at the same time as other live vaccines, but if not administered simultaneously there should be a 4 week interval

Contraindications

- previous BCG vaccination
- a past history of tuberculosis
- HIV
- pregnancy
- positive tuberculin test (Heaf or Mantoux)

The BCG vaccine is not given to anyone over the age of 35, as there is no evidence that it works for people of this age group.

# TETANUS: VACCINATION

The tetanus vaccine is a cell-free purified toxin that is normally given as part of a combined vaccine.

Tetanus vaccine is currently given in the UK as part of the routine immunisation schedule at:

- 2 months
- 3 months
- 4 months
- 3-5 years
- 13-18 years

This therefore provides 5 doses of tetanus-containing vaccine. Five doses is now considered to provide adequate long-term protection against tetanus.

Intramuscular human tetanus immunoglobulin should be given to patients with high-risk wounds (e.g. Compound fractures, delayed surgical intervention, significant degree of devitalised tissue) irrespective of whether 5 doses of tetanus vaccine have previously been given

If vaccination history is incomplete or unknown then a dose of tetanus vaccine should be given combined with intramuscular human tetanus immunoglobulin for high-risk wounds

# HIV: IMMUNISATION

The Department of Health 'Greenbook' on immunisation defers to the British HIV Association for guidelines relating to immunisation of HIV-infected adults

| Vaccines that can be used in all HIV-infected adults | Vaccines that can be used if CD4 > 200 | Contraindicated in HIV-infected adults |
|---|---|---|
| Hepatitis A<br>Hepatitis B<br>*Haemophilus influenzae* B (Hib)<br>Influenza-parenteral<br>Japanese encephalitis<br>Meningococcus-MenC<br>Meningococcus-ACWY I<br>Pneumococcus-PPV23<br>Poliomyelitis-parenteral (IPV)<br>Rabies<br>Tetanus-Diphtheria (Td) | Measles, Mumps, Rubella (MMR)<br>Varicella<br>Yellow Fever | Cholera CVD103-HgR<br>Influenza-intranasal<br>Poliomyelitis-oral (OPV)<br>Tuberculosis (BCG) |

# POST-EXPOSURE PROPHYLAXIS

Hepatitis A

- Human Normal Immunoglobulin (HNIG) or hepatitis A vaccine may be used depending on the clinical situation

Hepatitis B

- HBsAg positive source: if the person exposed is a known responder to HBV vaccine then a booster dose should be given. If they are in the process of being vaccinated or are a non-responder they need to have hepatitis B immune globulin (HBIG) and the vaccine
- unknown source: for known responders the green book advises considering a booster dose of HBV vaccine. For known non-responders HBIG + vaccine should be given whilst those in the process of being vaccinated should have an accelerated course of HBV vaccine

Hepatitis C

- monthly PCR - if seroconversion then interferon +/- ribavirin

HIV

- the risk of HIV transmission depends heavily on the incident (e.g. needle stick, type of sexual intercourse, human bite etc) and the current viral load of the patient
- please see the BHIVA link for charts which outline the risk depending on the incident. Generally, low-risk incidents such as human bites don't require post-exposure prophylaxis
- a combination of oral antiretrovirals (e.g. Tenofovir, emtricitabine, lopinavir and ritonavir) as soon as possible (i.e. Within 1-2 hours, but may be started up to 72 hours following exposure) for 4 weeks
- serological testing at 12 weeks following completion of post-exposure prophylaxis
- reduces risk of transmission by 80%

Varicella zoster

- VZIG for IgG negative pregnant women/immunosuppressed

**Estimates of transmission risk for single needlestick injury**

| Hepatitis B | 20-30% |
|---|---|
| Hepatitis C | 0.5-2% |
| HIV | 0.3% |

# ANTIBIOTICS: BACTERICIDAL VS. BACTERIOSTATIC

Bactericidal antibiotics
- penicillins
- cephalosporins
- aminoglycosides
- nitrofurantoin
- metronidazole
- quinolones
- rifampicin
- isoniazid

Bacteriostatic antibiotics
- chloramphenicol
- macrolides
- tetracyclines
- sulphonamides
- trimethoprim

# ANTIBIOTIC GUIDELINES

The following is based on current BNF guidelines:

**Respiratory system**

| Condition | Recommended treatment |
|---|---|
| Exacerbations of chronic bronchitis | Amoxicillin or tetracycline or clarithromycin |
| Uncomplicated community-acquired pneumonia | Amoxicillin (Doxycycline or clarithromycin in penicillin allergic, add flucloxacillin if staphylococci suspected e.g. In influenza) |
| Pneumonia possibly caused by atypical pathogens | Clarithromycin |
| Hospital-acquired pneumonia | Within 5 days of admission: co-amoxiclav or cefuroxime<br>More than 5 days after admission: piperacillin with tazobactam OR a broad-spectrum cephalosporin (e.g. ceftazidime) OR a quinolone (e.g. ciprofloxacin) |

**Urinary Tract**

| Condition | Recommended treatment |
|---|---|
| Lower urinary tract infection | Trimethoprim or nitrofurantoin. Alternative: amoxicillin or cephalosporin |
| Acute pyelonephritis | Broad-spectrum cephalosporin or quinolone |
| Acute prostatitis | Quinolone or trimethoprim |

## Skin

| Condition | Recommended treatment |
|---|---|
| Impetigo | Topical hydrogen peroxide, oral flucloxacillin or erythromycin if widespread |
| Cellulitis | Flucloxacillin (clarithromycin, erythromycin or doxycycline if penicillin-allergic) |
| Cellulitis (near the eyes or nose) | Co-amoxiclav (clarithromycin, + metronidazole if penicillin-allergic) |
| Erysipelas | Flucloxacillin* (clarithromycin, erythromycin or doxycycline if penicillin-allergic) |
| Animal or human bite | Co-amoxiclav (doxycycline + metronidazole if penicillin-allergic) |
| Mastitis during breast-feeding | Flucloxacillin |

## Ear, nose & throat

| Condition | Recommended treatment |
|---|---|
| Throat infections | Phenoxymethylpenicillin (erythromycin alone if penicillin-allergic) |
| Sinusitis | Amoxicillin or doxycycline or erythromycin |
| Otitis media | Amoxicillin (erythromycin if penicillin-allergic) |
| Otitis externa** | Flucloxacillin (erythromycin if penicillin-allergic) |
| Periapical or periodontal abscess | Amoxicillin |
| Gingivitis: acute necrotising ulcerative | Metronidazole |

## Genital system

| Condition | Recommended treatment |
|---|---|
| Gonorrhoea | Intramuscular ceftriaxone |
| *Chlamydia* | Doxycycline or azithromycin |
| Pelvic inflammatory disease | Oral ofloxacin + oral metronidazole or intramuscular ceftriaxone + oral doxycycline + oral metronidazole |
| Syphilis | Benzathine benzylpenicillin or doxycycline or erythromycin |
| Bacterial vaginosis | Oral or topical metronidazole or topical clindamycin |

## Gastrointestinal

| Condition | Recommended treatment |
|---|---|
| *Clostridium difficile* | First episode: metronidazole<br>Second or subsequent episode of infection: vancomycin |
| Campylobacter enteritis | Clarithromycin |
| Salmonella (non-typhoid) | Ciprofloxacin |
| Shigellosis | Ciprofloxacin |

*phenoxymethylpenicillin was previously the recommended antibiotic until the 2019 NICE guidelines

**a combined topical antibiotic and corticosteroid is generally used for mild/moderate cases of otitis externa

# ANTIFUNGAL AGENTS

| Drug | Mechanism of action | Adverse effects | Notes |
|---|---|---|---|
| Azoles | Inhibits 14α-demethylase which produces ergosterol | P450 inhibition<br>Liver toxicity | |
| Amphotericin B | Binds with ergosterol forming a transmembrane channel that leads to monovalent ion (K+, Na+, H+ and Cl) leakage | Nephrotoxicity, flu-like symptoms, hypokalaemia, hypomagnaseamia | Used for systemic fungal infections |
| Terbinafine | Inhibits squalene epoxidase | | Commonly used in oral form to treat fungal nail infections |
| Griseofulvin | Interacts with microtubules to disrupt mitotic spindle | Induces P450 system, teratogenic | |
| Flucytosine | Converted by cytosine deaminase to 5-fluorouracil, which inhibits thymidylate synthase and disrupts fungal protein synthesis | Vomiting | |
| Caspofungin | Inhibits synthesis of beta-glucan, a major fungal cell wall component | Flushing | |
| Nystatin | Binds with ergosterol forming a transmembrane channel that leads to monovalent ion (K+, Na+, H+ and Cl) leakage | | As very toxic can only be used topically (e.g. for oral thrush) |

# ANTIVIRAL AGENTS

| Drug | Mechanism of action | Indications | Adverse effects/toxicity |
|---|---|---|---|
| **Aciclovir** | Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase | HSV, VZV | Crystalline nephropathy |
| **Ganciclovir** | Guanosine analog, phosphorylated by thymidine kinase which in turn inhibits the viral DNA polymerase | CMV | Myelosuppression/agranulocytosis |
| **Ribavirin** | Guanosine analog which inhibits inosine monophosphate (IMP) dehydrogenase, interferes with the capping of viral mRNA | Chronic hepatitis C, RSV | Haemolytic anaemia |
| **Amantadine** | Inhibits uncoating (M2 protein) of virus in cell. Also releases dopamine from nerve endings | Influenza, Parkinson's disease | Confusion, ataxia, slurred speech |
| **Oseltamivir** | Inhibits neuraminidase | Influenza | |
| **Foscarnet** | Pyrophosphate analog which inhibits viiral DNA polymerase | CMV, HSV if not responding to aciclovir | Nephrotoxicity, hypocalcaemia, hypomagnasaemia, seizures |
| **Interferon-α** | Human glycoproteins which inhibit synthesis of mRNA | Chronic hepatitis B & C, hairy cell leukaemia | Flu-like symptoms, anorexia, myelosuppression |
| **Cidofovir** | Acyclic nucleoside phosphonate, and is therefore independent of phosphorylation by viral enzymes (compare and contrast with aciclovir/ganciclovir) | CMV retinitis in HIV | Nephrotoxicity |

**Anti-retroviral agent used in HIV**

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), didanosine, lamivudine, stavudine, zalcitabine

Protease inhibitors (PI)

- inhibits a protease needed to make the virus able to survive outside the cell
- examples: indinavir, nelfinavir, ritonavir, saquinavir

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz

# PASSMEDICINE NOTES NEPHROLOGY

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# ERYTHROPOIETIN

Erythropoietin is a haematopoietic growth factor that stimulates the production of erythrocytes. Erythropoietin is secreted by the kidney in response to cellular hypoxia. The main uses of erythropoietin are to treat the anaemia associated with chronic kidney disease and that associated with cytotoxic therapy.

Side-effects of erythropoietin

- accelerated hypertension potentially leading to encephalopathy and seizures (blood pressure increases in 25% of patients)
- bone aches
- flu-like symptoms
- skin rashes, urticaria
- pure red cell aplasia* (due to antibodies against erythropoietin)
- raised PCV increases risk of thrombosis (e.g. Fistula)
- iron deficiency 2nd to increased erythropoiesis

There are a number of reasons why patients may fail to respond to erythropoietin therapy:

- iron deficiency
- inadequate dose
- concurrent infection/inflammation
- hyperparathyroid bone disease
- aluminium toxicity

*the risk is greatly reduced with darbepoetin

# POLYURIA

A recent review in the BMJ categorised the causes of polyuria by how common they were. This does not of course tally with how common they are in exams!

Common (>1 in 10)

- diuretics, caffeine & alcohol
- diabetes mellitus
- lithium
- heart failure

Infrequent (1 in 100)

- hypercalcaemia
- hyperthyroidism

Rare (1 in 1000)

- chronic renal failure
- primary polydipsia
- hypokalaemia

Very rare (<1 in 10 000)
- diabetes insipidus

Jakes A, Bhandari S. Investigating polyuria. BMJ 2013;347:f6772.

# HAEMATURIA

The management of patients with haematuria is often difficult due to the absence of widely followed guidelines. It is sometimes unclear whether patients are best managed in primary care, by urologists or by nephrologists.

The terminology surrounding haematuria is changing. Microscopic or dipstick positive haematuria is increasingly termed non-visible haematuria whilst macroscopic haematuria is termed visible haematuria. Non-visible haematuria is found in around 2.5% of the population.

Causes of transient or spurious non-visible haematuria
- urinary tract infection
- menstruation
- vigorous exercise (this normally settles after around 3 days)
- sexual intercourse

Causes of persistent non-visible haematuria
- cancer (bladder, renal, prostate)
- stones
- benign prostatic hyperplasia
- prostatitis
- urethritis e.g. Chlamydia
- renal causes: IgA nephropathy, thin basement membrane disease

Spurious causes - red/orange urine, where blood is not present on dipstick
- foods: beetroot, rhubarb
- drugs: rifampicin, doxorubicin

**Management**
Current evidence does not support screening for haematuria. The incidence of non-visible haematuria is similar in patients taking aspirin/warfarin to the general population hence these patients should also be investigated.

Testing
- urine dipstick is the test of choice for detecting haematuria
- persistent non-visible haematuria is often defined as blood being present in 2 out of 3 samples tested 2-3 weeks apart
- renal function, albumin:creatinine (ACR) or protein:creatinine ratio (PCR) and blood pressure should also be checked
- urine microscopy may be used but time to analysis significantly affects the number of red blood cells detected

NICE urgent cancer referral guidelines were updated in 2015.

**Urgent referral (i.e. within 2 weeks)**
- Aged >= 45 years AND:
- unexplained visible haematuria without urinary tract infection, or
- visible haematuria that persists or recurs after successful treatment of urinary tract infection

Aged >= 60 years AND have unexplained nonvisible haematuria and either dysuria or a raised white cell count on a blood test

**Non-urgent referral**
Aged 60 >= 60 years with recurrent or persistent unexplained urinary tract infection

Since the investigation (or not) of non-visible haematuria is such as a common dilemma a number of guidelines have been published. They generally agree with NICE guidance, of note:
- patients under the age of 40 years with normal renal function, no proteinuria and who are normotensive do not need to be referred and may be managed in primary care

# HAEMOLYTIC URAEMIC SYNDROME

Haemolytic uraemic syndrome is generally seen in young children and produces a triad of:
- acute kidney injury
- microangiopathic haemolytic anaemia
- thrombocytopenia

Most cases are secondary (termed 'typical HUS'):
- classically Shiga toxin-producing Escherichia coli (STEC) 0157:H7 ('verotoxigenic', 'enterohaemorrhagic'). This is the most common cause in children, accounting for over 90% of cases
- pneumococcal infection
- HIV
- rare: systemic lupus erythematosus, drugs, cancer

Primary HUS ('atypical') is due to complement dysregulation.

Investigations
- full blood count: anaemia, thrombocytopaenia, fragmented blood film
- U&E: acute kidney injury
- stool culture

Management
- treatment is supportive e.g. Fluids, blood transfusion and dialysis if required
- there is no role for antibiotics, despite the preceding diarrhoeal illness in many patients
- the indications for plasma exchange in HUS are complicated. As a general rule plasma exchange is reserved for severe cases of HUS not associated with diarrhoea
- eculizumab (a C5 inhibitor monoclonal antibody) has evidence of greater efficiency than plasma exchange alone in the treatment of adult atypical HUS

# RHABDOMYOLYSIS

Rhabdomyolysis will typically feature in the exam as a patient who has had a fall or prolonged epileptic seizure and is found to have an acute kidney injury on admission.

Features
- acute kidney injury with disproportionately raised creatinine
- elevated creatine kinase (CK)
- myoglobinuria
- hypocalcaemia (myoglobin binds calcium)
- elevated phosphate (released from myocytes)
- hyperkalaemia (may develop before renal failure)
- metabolic acidosis

Causes
- seizure
- collapse/coma (e.g. elderly patients collapses at home, found 8 hours later)
- ecstasy
- crush injury
- McArdle's syndrome
- drugs: statins (especially if co-prescribed with clarithromycin)

Management
- IV fluids to maintain good urine output
- urinary alkalinization is sometimes used

# ACUTE INTERSTITIAL NEPHRITIS

Acute interstitial nephritis accounts for 25% of drug-induced acute kidney injury.

Causes

- drugs: the most common cause, particularly antibiotics
    - penicillin
    - rifampicin
    - NSAIDs
    - allopurinol
    - furosemide
- systemic disease: SLE, sarcoidosis, and Sjögren's syndrome
- infection: Hanta virus , staphylococci

Pathophysiology

- histology: marked interstitial oedema and interstitial infiltrate in the connective tissue between renal tubules

Features

- fever, rash, arthralgia
- eosinophilia
- mild renal impairment
- hypertension

Investigations

- sterile pyuria
- white cell casts

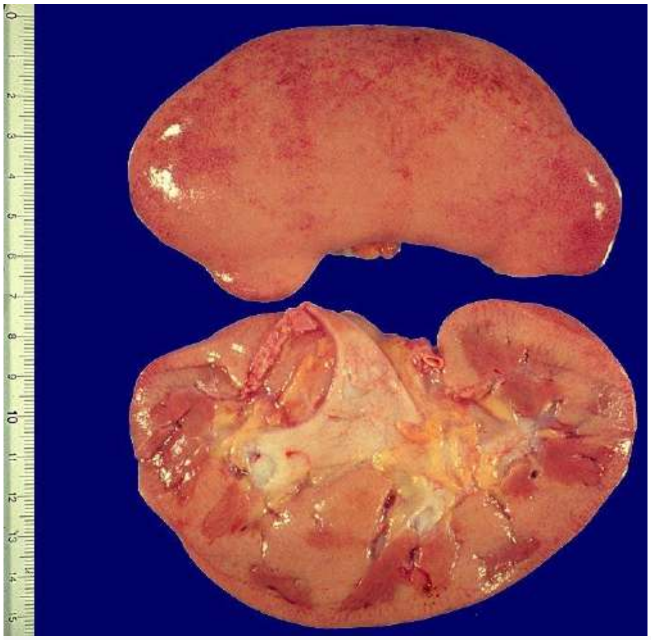
**Tubulointerstitial nephritis with uveitis**

Tubulointerstitial nephritis with uveitis (TINU) usually occurs in young females. Symptoms include fever, weight loss and painful, red eyes. Urinalysis is positive for leukocytes and protein.

# ACUTE KIDNEY INJURY: A VERY BASIC INTRODUCTION

Acute kidney injury (AKI), previously termed acute renal failure, describes a reduction in renal function following an insult to the kidneys. In years gone by the kidneys were very much a neglected organ in acute medicine - the recognition of decreasing renal function was often slow and action limited. Around 15% of patients admitted to hospital develop AKI.

Whilst most patients with AKI recover their renal function there are many patients who will have long term impaired kidney function due to AKI. As well as long-term morbidity, AKI may also result in acute complications including death. Whilst exact figures are difficult to calculate NICE estimate that inpatient mortality of AKI in the UK might typically be 25-30% or more.



Specimen from a patient who had an acute kidney injury. Note the marked pallor of the cortex in certain areas, contrasting to the darker areas of surviving medullary tissue.

**What causes AKI?**

Causes of AKI are traditionally divided into prerenal, intrinsic and postrenal causes

**Prerenal**

Think of what causes big problems in other major organs. In the heart a lack of blood (ischaemia) to the myocardium causes a myocardial infarction. In a similar fashion 85% of strokes are causes be ischaemia to the brain. The same goes for the kidneys. One of the major causes of AKI is ischaemia, or lack of blood flowing to the kidneys.

Examples

- hypovolaemia secondary to diarrhoea/vomiting
- renal artery stenosis

**Intrinsic**
The second group of causes relate to intrinsic damage to the glomeruli, renal tubules or interstitium of the kidneys themselves. This may be due to toxins (drugs, contrast etc) or immune-mediated glomuleronephritis.

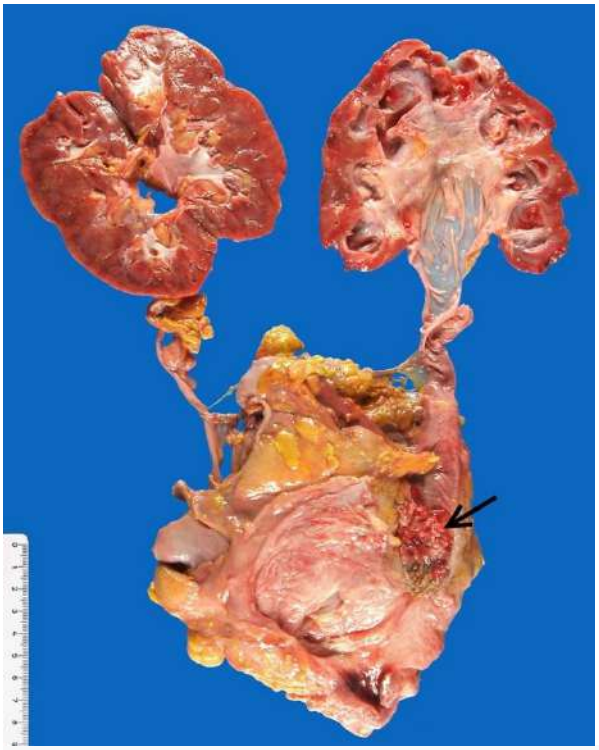
Examples

- glomerulonephritis
- acute tubular necrosis (ATN)
- acute interstitial nephritis (AIN), respectively
- rhabdomyolysis
- tumour lysis syndrome

**Postrenal**
The third group relates to problems after the kidneys. This is where there is an obstruction to the urine coming from the kidneys resulting in things 'backing-up' and affecting the normal renal function. An example could be a unilateral ureteric stone or bilateral hydroneprosis secondary to acute urinary retention caused by benign prostatic hyperplasia.

Examples

- kidney stone in ureter or bladder
- benign prostatic hyperplasia
- external compression of the ureter



This patient had an invasive papillary tumour of the distal left ureter, indicated by the arrow. This resulted in the ureter becoming blocked, resulting in a left hydroureter and hydronephrosis. Note the thinning of the renal cortex of the left kidney compared to the right.

**Who is at an increased risk of AKI?**
One of the keys to reducing the incidence of AKI is identifying patient who are at increased risk. NICE support this approach and have published guidelines suggesting which patients are at greater risk.

Risk factors for AKI include:

- chronic kidney disease
- other organ failure/chronic disease e.g. heart failure, liver disease, diabetes mellitus
- history of acute kidney injury
- use of drugs with nephrotoxic potential (e.g. NSAIDs, aminoglycosides, ACE inhibitors, angiotensin II receptor antagonists [ARBs] and diuretics) within the past week
- use of iodinated contrast agents within the past week
- age 65 years or over
- oliguria (urine output less than 0.5 ml/kg/hour)
- neurological or cognitive impairment or disability, which may mean limited access to fluids because of reliance on a carer

**Preventing AKI**
By identifying patients at increased risk of AKI (see above) it may be possible to take steps to reduce the risk. For example, patients who are at risk of AKI and who are undergoing an investigation requiring contrast are usually given IV fluids to reduce the risk. Certain drugs such as ACE inhibitors and ARBs may also be temporarily stopped.

**What happens when kidneys stop working?**
It's best to work backwards and think about what kidneys actually do. The kidneys are primarily responsible for fluid balance and maintaining homeostasis. Therefore two of the key ways AKI may be detected are:

- a reduced urine output. This is termed oliguria and is defined as a urine output of less than 0.5 ml/kg/hour
- fluid overload
- a rise in molecules that the kidney normal excretes/maintains a careful balance of. Examples include potassium, urea and creatinine

**Symptoms and signs**
Many patients with early AKI may experience no symptoms. However, as renal failure progresses the following may be seen:

- reduced urine output
- pulmonary and peripheral oedema
- arrhythmias (secondary to changes in potassium and acid-base balance)
- features of uraemia (for example, pericarditis or encephalopathy)

**Detection**
One of the most common blood tests performed on the wards is 'urea and electrolytes' or 'U&Es'. This returns a number of markers, including

- sodium
- potassium
- urea
- creatinine

NICE recommend that we can use a variety of different criteria to make an official diagnosis of AKI. They state:

Detect acute kidney injury, in line with the (p)RIFLE, AKIN or KDIGO definitions, by using any of the following criteria:

- *a rise in serum creatinine of 26 micromol/litre or greater within 48 hours*
- *a 50% or greater rise in serum creatinine known or presumed to have occurred within the past 7 days*
- *a fall in urine output to less than 0.5 ml/kg/hour for more than 6 hours in adults and more than*

Urinanalysis

- all patients with suspected AKI should have urinanalysis

Imaging

- if patients have no identifiable cause for the deterioration or are at risk of urinary tract obstruction they should have a renal ultrasound within 24 hours of assessment.

**Management**

The management of AKI is largely supportive. This means patients require careful fluid balance to ensure that the kidneys are properly perfused but not excessively to avoid fluid overload. It is also important to review a patient's medication list to see what treatments may either be exacerbating their renal dysfunction or may be dangerous as a consequence of renal dysfunction. The table below gives some examples of common drugs:

| Usually safe to continue in AKI | Should be stopped in AKI as may worsen renal function | May have to be stopped in AKI as increased risk of toxicity (but doesn't usually worsen AKI itself) |
|---|---|---|
| • Paracetamol<br>• Warfarin<br>• Statins<br>• Aspirin (at a cardioprotective dose of 75mg od)<br>• Clopidogrel<br>• Beta-blockers | • NSAIDs (except if aspirin at cardiac dose e.g. 75mg od)<br>• Aminoglycosides<br>• ACE inhibitors<br>• Angiotensin II receptor antagonists<br>• Diuretics | • Metformin<br>• Lithium<br>• Digoxin |

Treatments which are **not recommend** include the routine use of loop diuretics (to artificially boost urine output) and low-dose dopamine (in an attempt to increase renal perfusion). There is however a role for loop diuretics in patients who experience significant fluid overload.

Hyperkalaemia also needs prompt treatment to avoid arrhythmias which may potentially be life-threatening. The table below categorises the different treatments for hyperkalaemia:

| Stabilisation of the cardiac membrane | • Short-term shift in potassium from extracellular to intracellular fluid compartment | • Removal of potassium from the body |
|---|---|---|
| • Intravenous calcium gluconate | • Combined insulin/dextrose infusion<br>• Nebulised salbutamol | • Calcium resonium (orally or enema)<br>• Loop diuretics<br>• Dialysis |

Specialist input from a nephrologist is required for cases where the cause is not known or where the AKI is severe.

All patients with suspected AKI secondary to urinary obstruction require prompt review by a urologist.

Renal replacement therapy (e.g. haemodialysis) is used when a patient is not responding to medical treatment of complications, for example hyperkalaemia, acidosis or uraemia.

## ACUTE KIDNEY INJURY: NICE GUIDELINES

This guideline tells what increases the risk of AKI:
1. Emergency surgery, ie, risk of sepsis or hypovolaemia
2. Intraperitoneal surgery
3. CKD, ie if eGFR < 60
4. Diabetes
5. Heart failure
6. Age >65 years
7. Liver disease
8. Use of nephrotoxic drugs

It also defines the criteria for diagnosing AKI
1. Rise in creatinine of 26 micromol/L or more in 48 hours OR
2. >= 50% rise in creatinine over 7 days OR
3. Fall in urine output to less than 0.5ml/kg/hour for more than 6 hours in adults (8 hours in children) OR
4. >= 25% fall in eGFR in children / young adults in 7 days.

Refer to a nephrologist if any of the following apply:
1. Renal tranplant
2. ITU patient with unknown cause of AKI
3. Vasculitis/ glomerulonephritis/ tubulointerstitial nephritis/ myeloma
4. AKI with no known cause

5. Inadequate response to treatment
6. Complications of AKI
7. Stage 3 AKI (see guideline for details)
8. CKD stage 4 or 5
9. Qualify for renal replacement hyperkalaemia / metabolic acidosis/ complications of uraemia/ fluid overload (pulmonary oedema)

# CHRONIC KIDNEY DISEASE: CAUSES

Common causes of chronic kidney disease
- diabetic nephropathy
- chronic glomerulonephritis
- chronic pyelonephritis
- hypertension
- adult polycystic kidney disease

# FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Focal segmental glomerulosclerosis (FSGS) is a cause of nephrotic syndrome and chronic kidney disease. It generally presents in young adults.

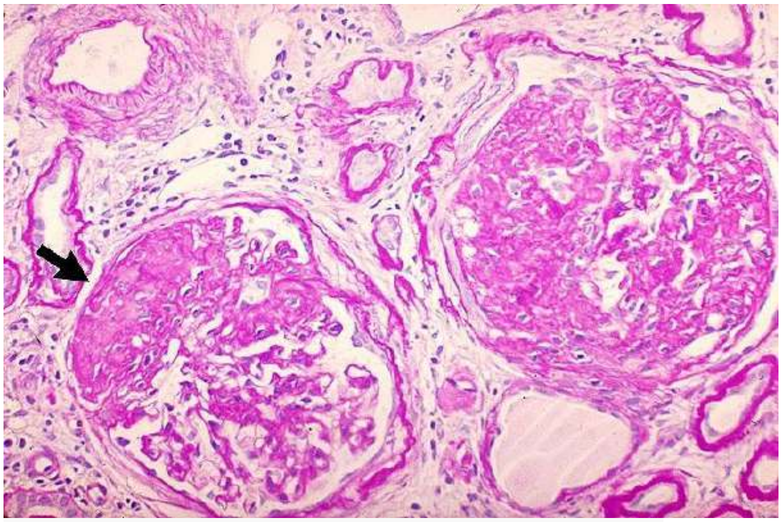
Causes
- idiopathic
- secondary to other renal pathology e.g. IgA nephropathy, reflux nephropathy
- HIV
- heroin
- Alport's syndrome
- sickle-cell

Focal segmental glomerulosclerosis is noted for having a high recurrence rate in renal transplants.

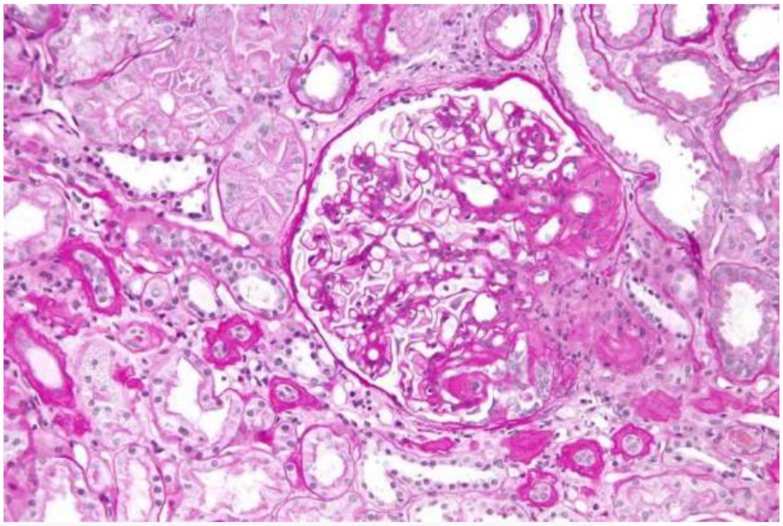
Investigations
- renal biopsy
    - focal and segmental sclerosis and hyalinosis on light microscopy
    - effacement of foot processes on electron microscopy

Management
- steroids +/- immunosuppressants

Prognosis
- untreated FSGS has a < 10% chance of spontaneous remission



Sclerosis of the glomerulus is seen next to Bowman's capsule



Sclerosis is seen in the perihilar region of the glomerulus

## CHRONIC KIDNEY DISEASE: EGFR AND CLASSIFICATION

Serum creatinine may not provide an accurate estimate of renal function due to differences in muscle. For this reason formulas were develop to help estimate the glomerular filtration rate (estimated GFR or eGFR). The most commonly used formula is the Modification of Diet in Renal Disease (MDRD) equation, which uses the following variables:

- serum creatinine
- age
- gender
- ethnicity

Factors which may affect the result

- pregnancy
- muscle mass (e.g. amputees, body-builders)
- eating red meat 12 hours prior to the sample being taken

CKD may be classified according to GFR:

| CKD stage | GFR range |
|---|---|
| 1 | Greater than 90 ml/min, with some sign of kidney damage on other tests (if all the kidney tests* are normal, there is no CKD) |
| 2 | 60-90 ml/min with some sign of kidney damage (if kidney tests* are normal, there is no CKD) |
| 3a | 45-59 ml/min, a moderate reduction in kidney function |
| 3b | 30-44 ml/min, a moderate reduction in kidney function |
| 4 | 15-29 ml/min, a severe reduction in kidney function |
| 5 | Less than 15 ml/min, established kidney failure - dialysis or a kidney transplant may be needed |

*i.e. normal U&Es and no proteinuria

# CHRONIC KIDNEY DISEASE: HYPERTENSION

The majority of patients with chronic kidney disease (CKD) will require more than two drugs to treat hypertension. ACE inhibitors are first line and are particularly helpful in proteinuric renal disease (e.g. diabetic nephropathy). As these drugs tend to reduce filtration pressure a small fall in glomerular filtration pressure (GFR) and rise in creatinine can be expected. NICE suggest that a decrease in eGFR of up to 25% or a rise in creatinine of up to 30% is acceptable, although any rise should prompt careful monitoring and exclusion of other causes (e.g. NSAIDs). A rise greater than this may indicate underlying renovascular disease.

Furosemide is useful as a anti-hypertensive in patients with CKD, particularly when the GFR falls to below 45 ml/min*. It has the added benefit of lowering serum potassium. High doses are usually required. If the patient becomes at risk of dehydration (e.g. Gastroenteritis) then consideration should be given to temporarily stopping the drug

*the NKF K/DOQI guidelines suggest a lower cut-off of less than 30 ml/m

# CHRONIC KIDNEY DISEASE: ANAEMIA

Patients with chronic kidney disease (CKD) may develop anaemia due to a variety of factors, the most significant of which is reduced erythropoietin levels. This is usually a normochromic normocytic anaemia and becomes apparent when the GFR is less than 35 ml/min (other causes of anaemia should be considered if the GFR is > 60 ml/min). Anaemia in CKD predisposes to the development of left ventricular hypertrophy - associated with a three fold increase in mortality in renal patients

Causes of anaemia in renal failure

- reduced erythropoietin levels - the most significant factor
- reduced erythropoiesis due to toxic effects of uraemia on bone marrow

- reduced absorption of iron
- anorexia/nausea due to uraemia
- reduced red cell survival (especially in haemodialysis)
- blood loss due to capillary fragility and poor platelet function
- stress ulceration leading to chronic blood loss

Management
- the 2011 NICE guidelines suggest a target haemoglobin of 10 - 12 g/dl
- determination and optimisation of iron status should be carried out prior to the administration of erythropoiesis-stimulating agents (ESA). Many patients, especially those on haemodialysis, will require IV iron
- ESAs such as erythropoietin and darbepoetin should be used in those 'who are likely to benefit in terms of quality of life and physical function'

# CHRONIC KIDNEY DISEASE: PROTEINURIA

Proteinuria is an important marker of chronic kidney disease, especially for diabetic nephropathy. NICE recommend using the albumin:creatinine ratio (ACR) in preference to the protein:creatinine ratio (PCR) when identifying patients with proteinuria as it has greater sensitivity. For quantification and monitoring of proteinuria, PCR can be used as an alternative, although ACR is recommended in diabetics. Urine reagent strips are not recommended unless they express the result as an ACR

**Approximate equivalent values**

| ACR (mg/mmol) | PCR (mg/mmol) | Urinary protein excretion (g/24 h) |
|---|---|---|
| 30 | 50 | 0.5 |
| 70 | 100 | 1 |

Collecting an ACR sample
- by collecting a 'spot' sample it avoids the need to collect urine over a 24 hour period in order to detect or quantify proteinuria
- should be a first-pass morning urine specimen
- if the initial ACR is between 3 mg/mmol and 70 mg/mmol, this should be confirmed by a subsequent early morning sample. If the initial ACR is 70 mg/mmol or more, a repeat sample need not be tested.

Interpreting the ACR results
- the NICE guidelines state 'regard a confirmed ACR of 3 mg/mmol or more as clinically important proteinuria'

NICE recommendations for referral to a nephrologist:
- a urinary albumin:creatinine ratio (ACR) of 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated
- a urinary ACR of 30 mg/mmol or more, together with persistent haematuria (two out of three dipstick tests show 1+ or more of blood) after exclusion of a urinary tract infection

- consider referral to a nephrologist for people with an ACR between 3-29 mg/mmol who have persistent haematuria and other risk factors such as a declining eGFR, or cardiovascular disease

**Frequency of monitoring eGFR (number of times per year by eGFR and ACR categories) for people with or at risk of CKD**

| eGFR categories (mL/min/1.73 m2) | ACR categories (mg/mmol) | | |
|---|---|---|---|
| | A1 (< 3) Normal to mildly increased | A2 (3-30) Moderately increased | A3 (> 30) Severely increased |
| G1 >=90 Normal and high | =< 1 | 1 | >= 1 |
| G2 60-89 Mild reduction related to normal range for a young adult | =< 1 | 1 | >= 1 |
| G3a 45-59 Mild to moderate reduction | 1 | 1 | 2 |
| G3b 30-44 Moderate to severe reduction | =< 2 | 2 | >= 2 |
| G4 15-29 Severe reduction | 2 | 2 | 3 |
| G5 <15 Kidney failure | 4 | >=4 | >=4 |

# CHRONIC KIDNEY DISEASE: BONE DISEASE

Basic problems in chronic kidney disease

- low vitamin D (1-alpha hydroxylation normally occurs in the kidneys)
- high phosphate
- low calcium: due to lack of vitamin D, high phosphate
- secondary hyperparathyroidism: due to low calcium, high phosphate and low vitamin D

Several clinical manifestations may result:

Osteitis fibrosa cystica

- aka hyperparathyroid bone disease

Adynamic

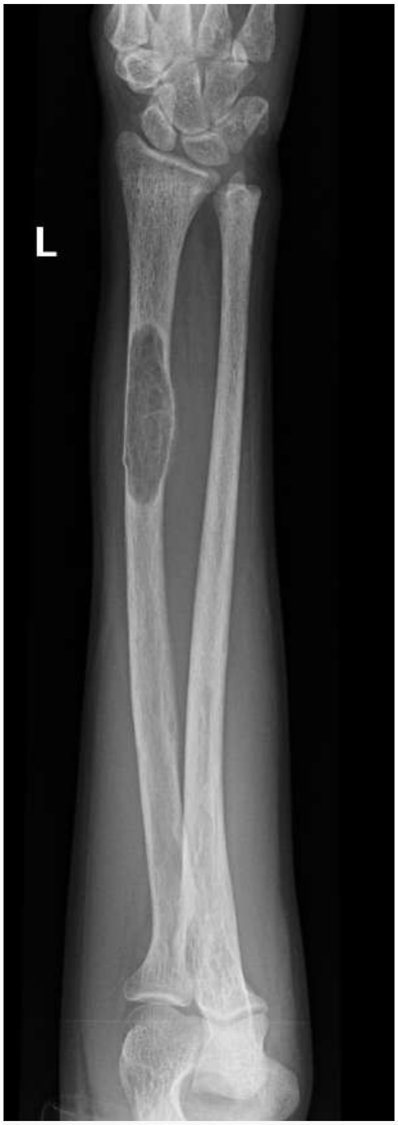
- reduction in cellular activity (both osteoblasts and osteoclasts) in bone
- may be due to over treatment with vitamin D

Osteomalacia

- due to low vitamin D

Osteosclerosis

Osteoporosis



X-ray of a Brown tumour caused by secondary hyperparathyroidism in a young female with chronic kidney disease

# CHRONIC KIDNEY DISEASE: MINERAL BONE DISEASE MANAGEMENT

**Pathophysiology**

Basic problems in chronic kidney disease (CKD):

- 1-alpha hydroxylation normally occurs in the kidneys → CKD leads to low vitamin D
- the kidneys normally excrete phosphate → CKD leads to high phosphate

This, in turn, causes other problems:

- the high phosphate level 'drags' calcium from the bones, resulting in osteomalacia
- low calcium: due to lack of vitamin D, high phosphate
- secondary hyperparathyroidism: due to low calcium, high phosphate and low vitamin D

**Management**
The aim is to reduce phosphate and parathyroid hormone levels.

Overview
- reduced dietary intake of phosphate is the first-line management
- phosphate binders
- vitamin D: alfacalcidol, calcitriol
- parathyroidectomy may be needed in some cases

Phosphate binders
- aluminium-based binders are less commonly used now
- calcium-based binders
    - problems include hypercalcemia and vascular calcification
- sevelamer
    - a non-calcium based binder that is now increasingly used
    - binds to dietary phosphate and prevents its absorption
    - also appears to have other beneficial effects including reducing uric acid levels and improving the lipid profiles of patients with chronic kidney disease

# CALCIPHYLAXIS

Calciphylaxis is a rare complication of end-stage renal failure. The underlying mechanism is not clear, however it results in deposition of calcium within arterioles causing microvascular occlusion and necrosis of the supplied tissue. It most commonly affects the skin and presents with painful necrotic skin lesions.

The risk of developing calciphylaxis is linked with hypercalcaemia, hyperphophataemia and hyperparathyroidism. Warfarin is widely reported as causing/exacerbating calciphylaxis in high risk patients, however the underlying mechanism is not known.

Treatment of calciphylaxis focuses on reducing calcium and phosphate levels, controlling hyperparathyroidism and avoiding contributing drugs such as warfarin and calcium containing compounds.

# GLOMERULONEPHRITIDES

Knowing a few key facts is the best way to approach the difficult subject of glomerulonephritis:

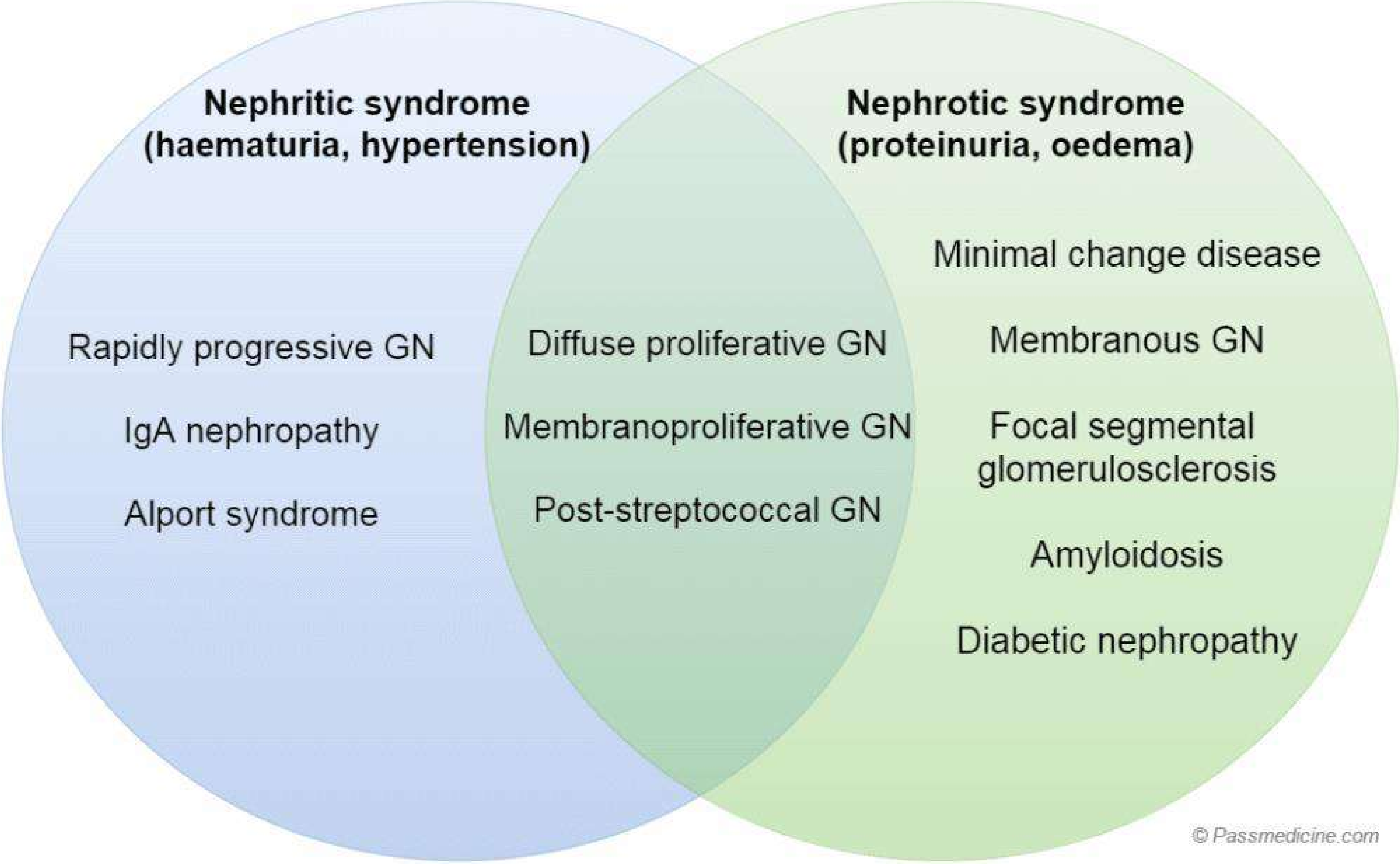

Nephritic syndrome
(haematuria, hypertension)
Nephrotic syndrome
(proteinuria, oedema)
Rapidly progressive GN
IgA nephropathy
Alport syndrome
Diffuse proliferative GN
Membranoproliferative GN
Post-streptococcal GN
Minimal change disease
Membranous GN
Focal segmental glomerulosclerosis
Amyloidosis
Diabetic nephropathy
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Diagram showing the glomerulonephritides and how they typically present

**Typically presents with nephritic syndrome (haematuria, hypertension)**
Rapidly progressive glomerulonephritis - aka crescentic glomerulonephritis

- rapid onset, often presenting as acute kidney injury
- causes include Goodpasture's, ANCA positive vasculitis

IgA nephropathy - aka Berger's disease, mesangioproliferative GN

- typically young adult with haematuria following an URTI

**Mixed nephritic/nephrotic presentation**
Diffuse proliferative glomerulonephritis

- classical post-streptococcal glomerulonephritis in child
- presents as nephritic syndrome / acute kidney injury
- most common form of renal disease in SLE

Membranoproliferative glomerulonephritis (mesangiocapillary)

- type 1: cryoglobulinaemia, hepatitis C
- type 2: partial lipodystrophy

**Typically presents with nephrotic syndrome (proteinuria, oedema)**

Minimal change disease
- typically a child with nephrotic syndrome (accounts for 80%)
- causes: Hodgkin's, NSAIDs
- good response to steroids

Membranous glomerulonephritis
- presentation: proteinuria / nephrotic syndrome / chronic kidney disease
- cause: infections, rheumatoid drugs, malignancy
- 1/3 resolve, 1/3 respond to cytotoxics, 1/3 develop chronic kidney disease

Focal segmental glomerulosclerosis
- may be idiopathic or secondary to HIV, heroin
- presentation: proteinuria / nephrotic syndrome / chronic kidney disease

# NEPHROTIC SYNDROME

Triad of:

1. Proteinuria (> 3g/24hr) causing
2. Hypoalbuminaemia (< 30g/L) and
3. Oedema

Loss of antithrombin-III, proteins C and S and an associated rise in fibrinogen levels predispose to thrombosis. Loss of thyroxine-binding globulin lowers the total, but not free, thyroxine levels.

# NEPHROTIC SYNDROME: CAUSES

Primary glomerulonephritis accounts for around 80% of cases
- minimal change glomerulonephritis (causes 80% in children, 30% in adults)
- membranous glomerulonephritis
- focal segmental glomerulosclerosis
- membranoproliferative glomerulonephritis

Systemic disease (about 20%)
  - diabetes mellitus
  - systemic lupus erythematosus
  - amyloidosis

Drugs
  - gold (sodium aurothiomalate), penicillamine

Others

- congenital
- neoplasia: carcinoma, lymphoma, leukaemia, myeloma
- infection: bacterial endocarditis, hepatitis B, malaria

# NEPHROTIC SYNDROME: COMPLICATIONS

Complications

- increased risk of infection due to urinary immunoglobulin loss
- increased risk of thromboembolism related to loss of antithrombin III and plasminogen in the urine. This may result in a renal vein thrombosis, resulting in a sudden deterioration in renal function
- hyperlipidaemia
- hypocalcaemia (vitamin D and binding protein lost in urine)
- acute renal failure

# SPIRONOLACTONE

Spironolactone is an aldosterone antagonist which acts in the cortical collecting duct.

Indications

- ascites: patients with cirrhosis develop a secondary hyperaldosteronism. Relatively large doses such as 100 or 200mg are often used
- hypertension: used in some patients as a NICE 'step 4' treatment
- heart failure (see RALES study below)
- nephrotic syndrome
- Conn's syndrome

Adverse effects

- hyperkalaemia
- gynaecomastia: less common with eplerenone

RALES

- NYHA III + IV, patients already taking ACE inhibitor
- low dose spironolactone reduces all cause mortality

# MEMBRANOUS GLOMERULONEPHRITIS

Membranous glomerulonephritis is the commonest type of glomerulonephritis in adults and is the third most common cause of end-stage renal failure (ESRF). It usually presents with nephrotic syndrome or proteinuria.

Renal biopsy demonstrates:

- electron microscopy: the basement membrane is thickened with subepithelial electron dense deposits. This creates a 'spike and dome' appearance

Causes

- idiopathic: due to anti-phospholipase A2 antibodies
- infections: hepatitis B, malaria, syphilis
- malignancy: lung cancer, lymphoma, leukaemia
- drugs: gold, penicillamine, NSAIDs
- autoimmune diseases: systemic lupus erythematosus (class V disease), thyroiditis, rheumatoid

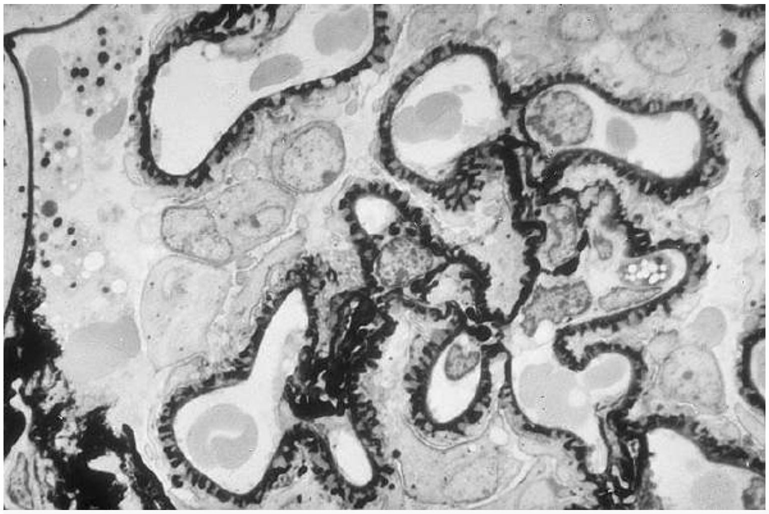
Management

- all patients should receive an ACE inhibitor or an angiotensin II receptor blocker (ARB):
    - these have been shown to reduce proteinuria and improve prognosis
- immunosuppression
    - as many patients spontaneously improve only patient with severe or progressive disease require immunosuppression
    - corticosteroids alone have not been shown to be effective. A combination of corticosteroid + another agent such as cyclophosphamide is often used
- consider anticoagulation for high-risk patients

Prognosis - rule of thirds

- one-third: spontaneous remission
- one-third: remain proteinuric
- one-third: develop ESRF

Good prognostic features include female sex, young age at presentation and asymptomatic proteinuria of a modest degree at the time of presentation.



Silver-stained section showing thickened basement membrane, subepithelial spikes

# MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Overview
- also known as mesangiocapillary glomerulonephritis
- may present as nephrotic syndrome, haematuria or proteinuria
- poor prognosis

Type 1
- accounts for 90% of cases
- cause: cryoglobulinaemia, hepatitis C
- renal biopsy
  - electron microscopy: subendothelial and mesangium immune deposits of electron-dense material resulting in a 'tram-track' appearance

Type 2 - 'dense deposit disease'
- causes: partial lipodystrophy (patients classically have a loss of subcutaneous tissue from their face), factor H deficiency
- caused by persistent activation of the alternative complement pathway
- low circulating levels of C3
- C3b nephritic factor is found in 70%
  - an antibody to alternative-pathway C3 convertase (C3bBb)
  - stabilizes C3 convertase
- renal biopsy
  - electron microscopy: intramembranous immune complex deposits with 'dense deposits'

Type 3
- causes: hepatitis B and C

Management
- steroids may be effective

# MINIMAL CHANGE DISEASE

Minimal change disease nearly always presents as nephrotic syndrome, accounting for 75% of cases in children and 25% in adults.

The majority of cases are idiopathic, but in around 10-20% a cause is found:
- drugs: NSAIDs, rifampicin
- Hodgkin's lymphoma, thymoma
- infectious mononucleosis

Pathophysiology

- T-cell and cytokine-mediated damage to the glomerular basement membrane → polyanion loss
- the resultant reduction of electrostatic charge → increased glomerular permeability to serum albumin

Features

- nephrotic syndrome
- normotension - hypertension is rare
- highly selective proteinuria
- only intermediate-sized proteins such as albumin and transferrin leak through the glomerulus
- renal biopsy
- normal glomeruli on light microscopy
- electron microscopy shows fusion of podocytes and effacement of foot processes

Management

- majority of cases (80%) are steroid-responsive
- cyclophosphamide is the next step for steroid-resistant cases

Prognosis is overall good, although relapse is common. Roughly:

- 1/3 have just one episode
- 1/3 have infrequent relapses
- 1/3 have frequent relapses which stop before adulthood

# GLOMERULONEPHRITIS AND LOW COMPLEMENT

Disorders associated with glomerulonephritis and low serum complement levels

- post-streptococcal glomerulonephritis
- subacute bacterial endocarditis
- systemic lupus erythematosus
- mesangiocapillary glomerulonephritis

# IGA NEPHROPATHY

IgA nephropathy (also known as Berger's disease) is the commonest cause of glomerulonephritis worldwide. It classically presents as macroscopic haematuria in young people following an upper respiratory tract infection.

Associated conditions

- alcoholic cirrhosis
- coeliac disease/dermatitis herpetiformis
- Henoch-Schonlein purpura

## Pathophysiology

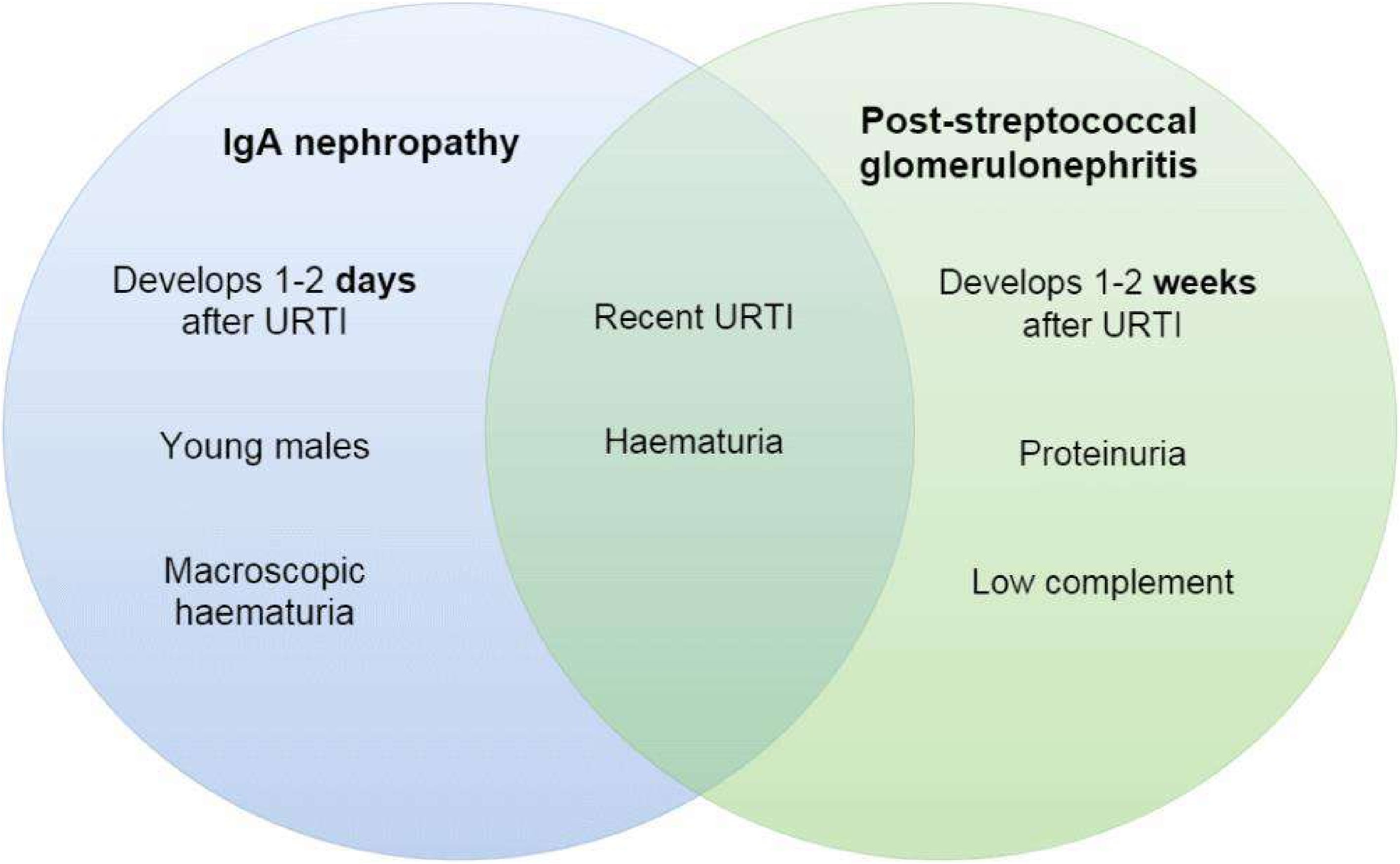
- thought to be caused by mesangial deposition of IgA immune complexes
- there is considerable pathological overlap with Henoch-Schonlein purpura (HSP)
- histology: mesangial hypercellularity, positive immunofluorescence for IgA & C3

## Presentations

- young male, recurrent episodes of macroscopic haematuria
- typically associated with a recent respiratory tract infection
- nephrotic range proteinuria is rare
- renal failure is unusual and seen in a minority of patients

## Differentiating between IgA nephropathy and post-streptococcal glomerulonephritis

- post-streptococcal glomerulonephritis is associated with low complement levels
- main symptom in post-streptococcal glomerulonephritis is proteinuria (although haematuria can occur)
- there is typically an interval between URTI and the onset of renal problems in post-streptococcal glomerulonephritis

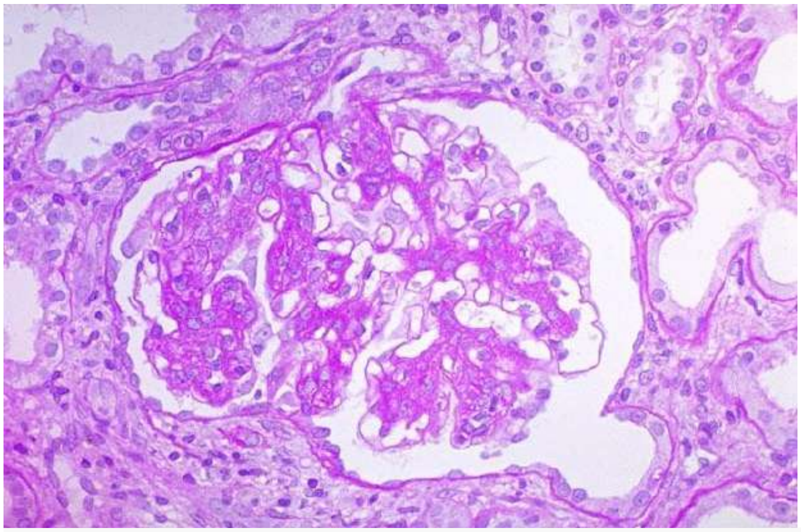

IgA nephropathy
Develops 1-2 days after URTI
Young males
Macroscopic haematuria
Recent URTI
Haematuria
Post-streptococcal glomerulonephritis
Develops 1-2 weeks after URTI
Proteinuria
Low complement

## Management

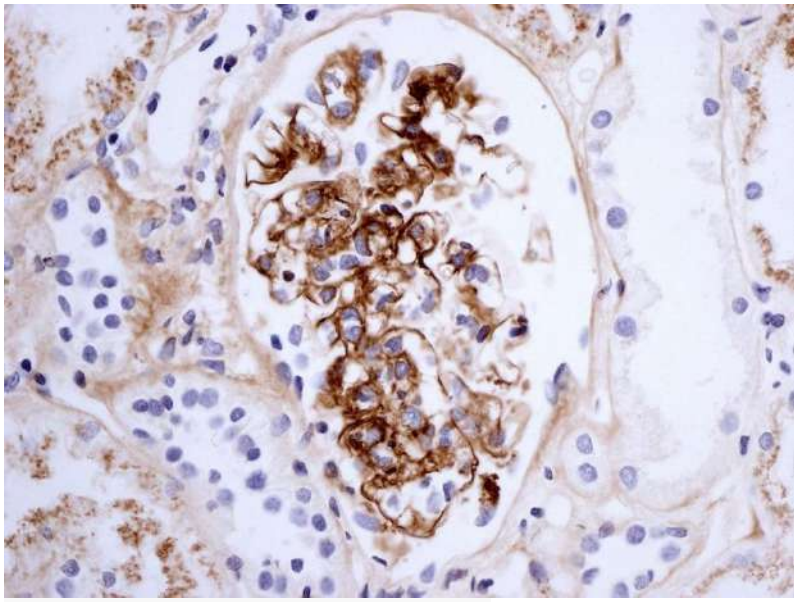
- steroids/immunosuppressants not be shown to be useful

Prognosis

- 25% of patients develop ESRF
- markers of good prognosis: frank haematuria
- markers of poor prognosis: male gender, proteinuria (especially > 2 g/day), hypertension, smoking, hyperlipidaemia, ACE genotype DD



Proliferation and hypercellularity of the mesangium is seen in the glomerulus



Immunostaining for IgA in a patient with HSP

## POST-STREPTOCOCCAL GLOMERULONEPHRITIS

Post-streptococcal glomerulonephritis typically occurs 7-14 days following a group A beta-haemolytic Streptococcus infection (usually Streptococcus pyogenes). It is caused by immune complex (IgG, IgM and C3) deposition in the glomeruli. Young children are most commonly affected.

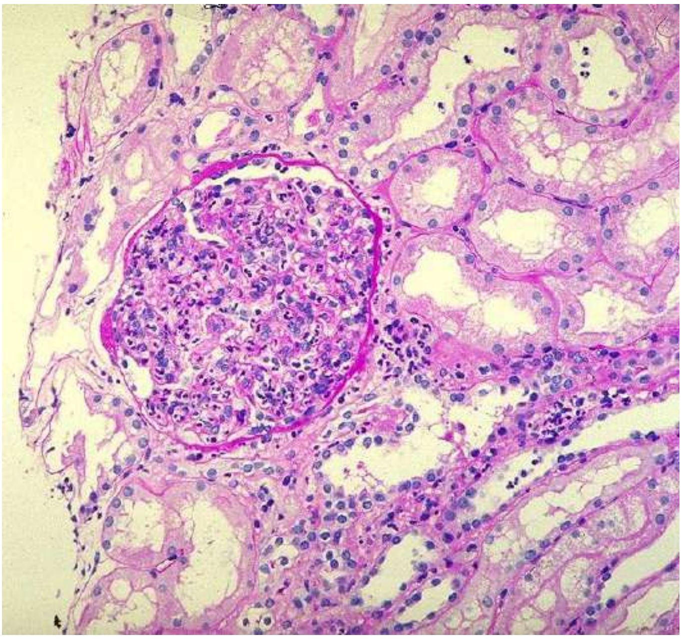
Features

- general: headache, malaise
- haematuria
- proteinuria
- hypertension
- low C3
- raised ASO titre

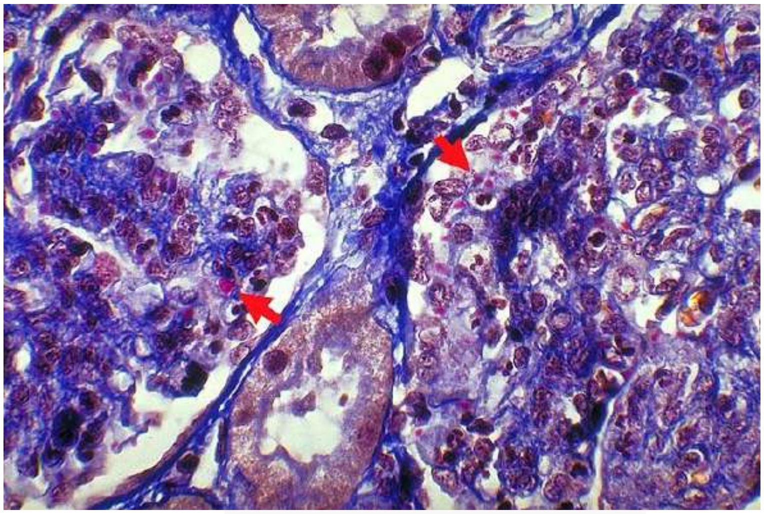
Renal biopsy features

- post-streptococcal glomerulonephritis causes acute, diffuse proliferative glomerulonephritis
- endothelial proliferation with neutrophils
- electron microscopy: subepithelial 'humps' caused by lumpy immune complex deposits
- immunofluorescence: granular or 'starry sky' appearance

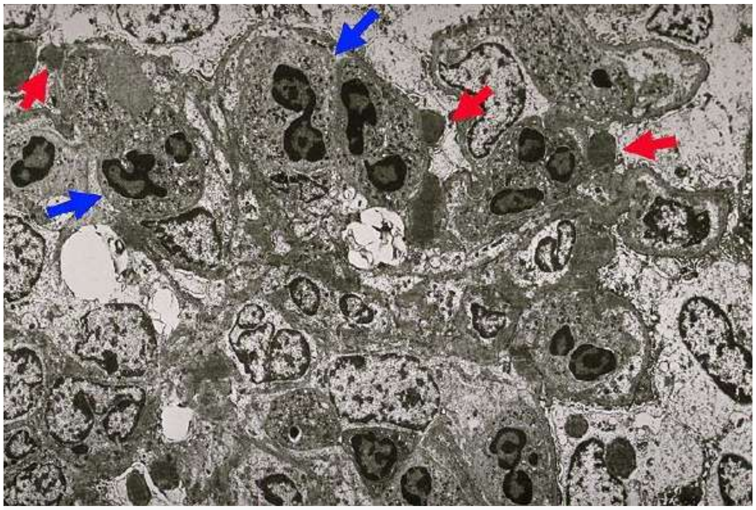
Carries a good prognosis



Proliferation of endothelium and mesangium with recruitment of neutrophils. Tubules are normal



Subepithelial humps on the outside of the basal membrane



Electron microscopy. Numerous neutrophils (blue arrows) and subepithelial humps(red arrows)

## RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

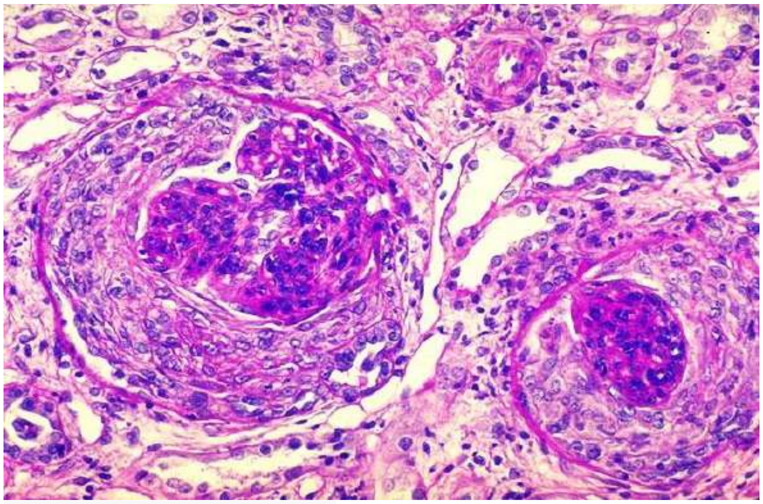
Rapidly progressive glomerulonephritis is a term used to describe a rapid loss of renal function associated with the formation of epithelial crescents in the majority of glomeruli.

Causes

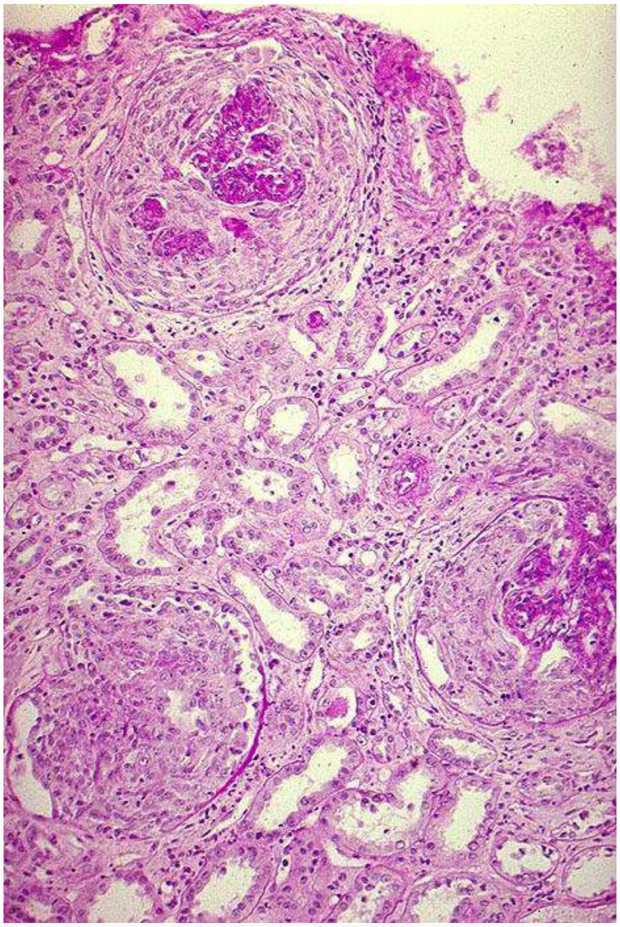
- Goodpasture's syndrome
- Wegener's granulomatosis
- others: SLE, microscopic polyarteritis

Features

- nephritic syndrome: haematuria with red cell casts, proteinuria, hypertension, oliguria
- features specific to underlying cause (e.g. haemoptysis with Goodpasture's, vasculitic rash or sinusitis with Wegener's)



Glomeruli are full of crescents.



Another image showing the glomeruli full of crescents

## GOODPASTURE'S SYNDROME

Goodpasture's syndrome is rare condition associated with both pulmonary haemorrhage and rapidly progressive glomerulonephritis. It is caused by anti-glomerular basement membrane (anti-GBM) antibodies against type IV collagen. Goodpasture's syndrome is more common in men (sex ratio 2:1) and has a bimodal age distribution (peaks in 20-30 and 60-70 age bracket). It is associated with HLA DR2.

Features
- pulmonary haemorrhage
- followed by rapidly progressive glomerulonephritis

Factors which increase the likelihood of pulmonary haemorrhage
- smoking
- lower respiratory tract infection
- pulmonary oedema
- inhalation of hydrocarbons
- young males

Investigations

- renal biopsy: linear IgG deposits along the basement membrane
- raised transfer factor secondary to pulmonary haemorrhages

Management

- plasma exchange (plasmapheresis)
- steroids
- cyclophosphamide

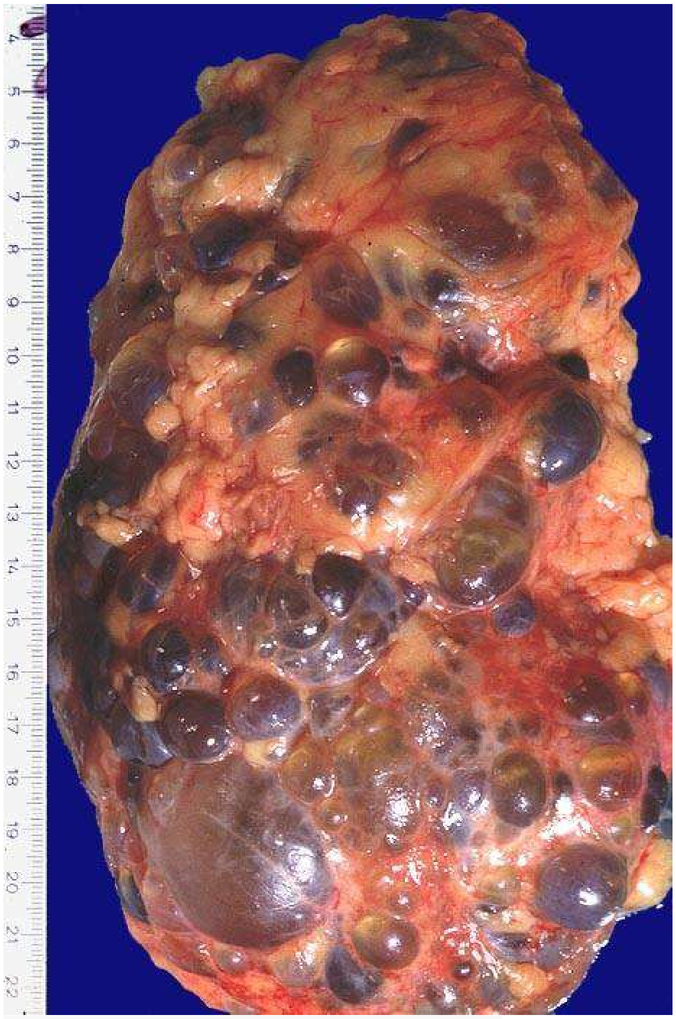
# ADPKD: FEATURES

Features

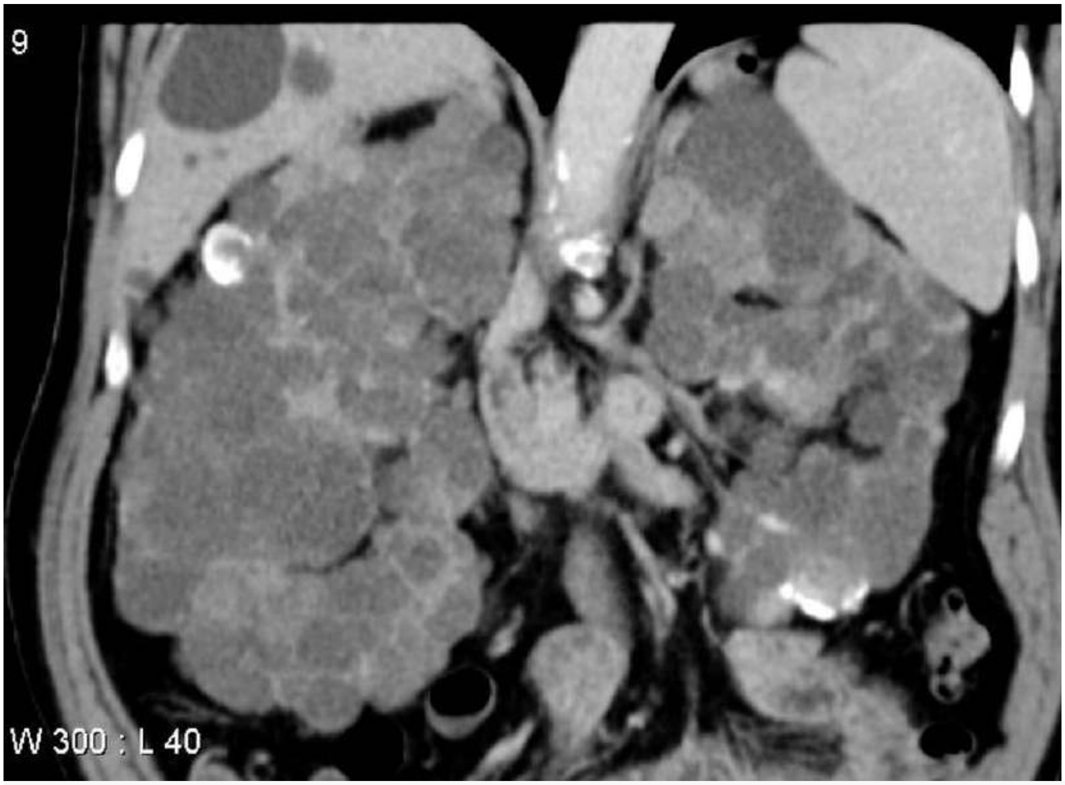
- hypertension
- recurrent UTIs
- abdominal pain
- renal stones
- haematuria
- chronic kidney disease

Extra-renal manifestations

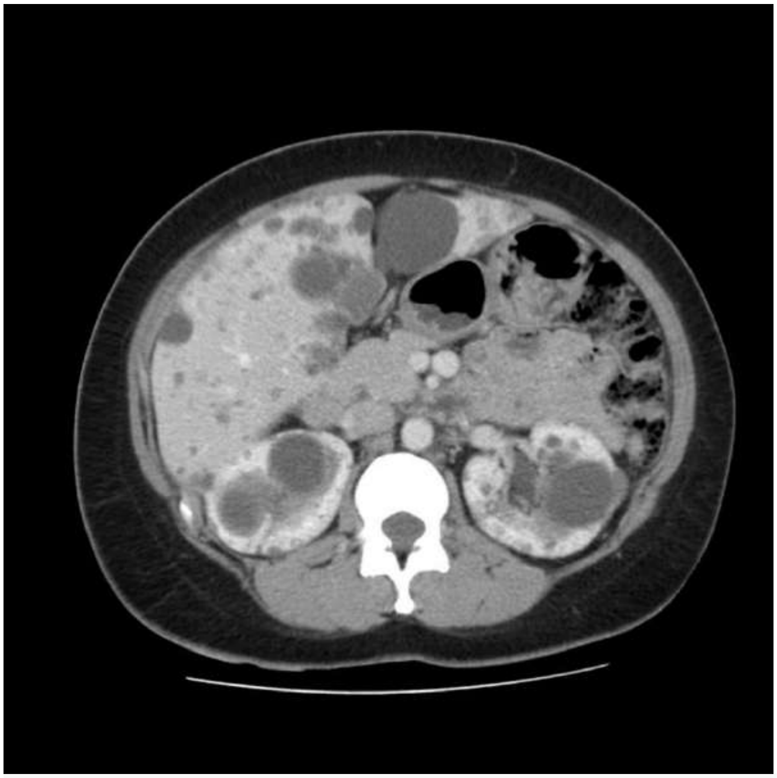
- liver cysts (70% - the commonest extra-renal manifestation): may cause hepatomegaly
- berry aneurysms (8%): rupture can cause subarachnoid haemorrhage
- cardiovascular system: mitral valve prolapse, mitral/tricuspid incompetence, aortic root dilation, aortic dissection
- cysts in other organs: pancreas, spleen; very rarely: thyroid, oesophagus, ovary



Extensive cysts are seen in an enlarged kidney



CT of the abdomen demonstrates both kidneys to be markedly enlarged by innumerable cysts ranging in size from a few millimeters to multiple centimeters with cysts also present in the liver



CT showing multiple cysts of varying sizes in the liver, and bilateral kidneys with little remaining normal renal parenchyma.

**ADPKD**

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of kidney disease, affecting 1 in 1,000 Caucasians. Two disease loci have been identified, PKD1 and PKD2, which code for polycystin-1 and polycystin-2 respectively

| ADPKD type 1 | ADPKD type 2 |
|---|---|
| 85% of cases | 15% of cases |
| Chromosome 16 | Chromosome 4 |
| Presents with renal failure earlier | |

The screening investigation for relatives is abdominal ultrasound:

Ultrasound diagnostic criteria (in patients with positive family history)
- two cysts, unilateral or bilateral, if aged < 30 years
- two cysts in both kidneys if aged 30-59 years
- four cysts in both kidneys if aged > 60 years

**Management**
For select patients, tolvaptan (vasopressin receptor 2 antagonist) may be an option. NICE recommended it as an option for treating ADPKD in adults to slow the progression of cyst development and renal insufficiency only if:
- they have chronic kidney disease stage 2 or 3 at the start of treatment
- there is evidence of rapidly progressing disease and
- the company provides it with the discount agreed in the patient access scheme.

# ARPKD

Autosomal recessive polycystic kidney disease (ARPKD) is much less common than autosomal dominant disease (ADPKD). It is due to a defect in a gene located on chromosome 6 which encodes fibrocystin, a protein important for normal renal tubule development.

Diagnosis may be made on prenatal ultrasound or in early infancy with abdominal masses and renal failure. Newborns may also have features consistent with Potter's syndrome secondary to oligohydramnios. End-stage renal failure develops in childhood. Patients also typically have liver involvement, for example portal and interlobular fibrosis.

Renal biopsy typically shows multiple cylindrical lesions at right angles to the cortical surface.

# AMYLOIDOSIS: TYPES

AL amyloidosis
- the most common form of amyloidosis
- L for immunoglobulin Light chain fragment
- due to myeloma, Waldenstrom's, MGUS
- features include: nephrotic syndrome, cardiac and neurological involvement, macroglossia, periorbital eccymoses

AA amyloid
- A for precursor serum amyloid A protein, an acute phase reactant
- seen in chronic infection/inflammation
- e.g. TB, bronchiectasis, rheumatoid arthritis
- features: renal involvement most common feature

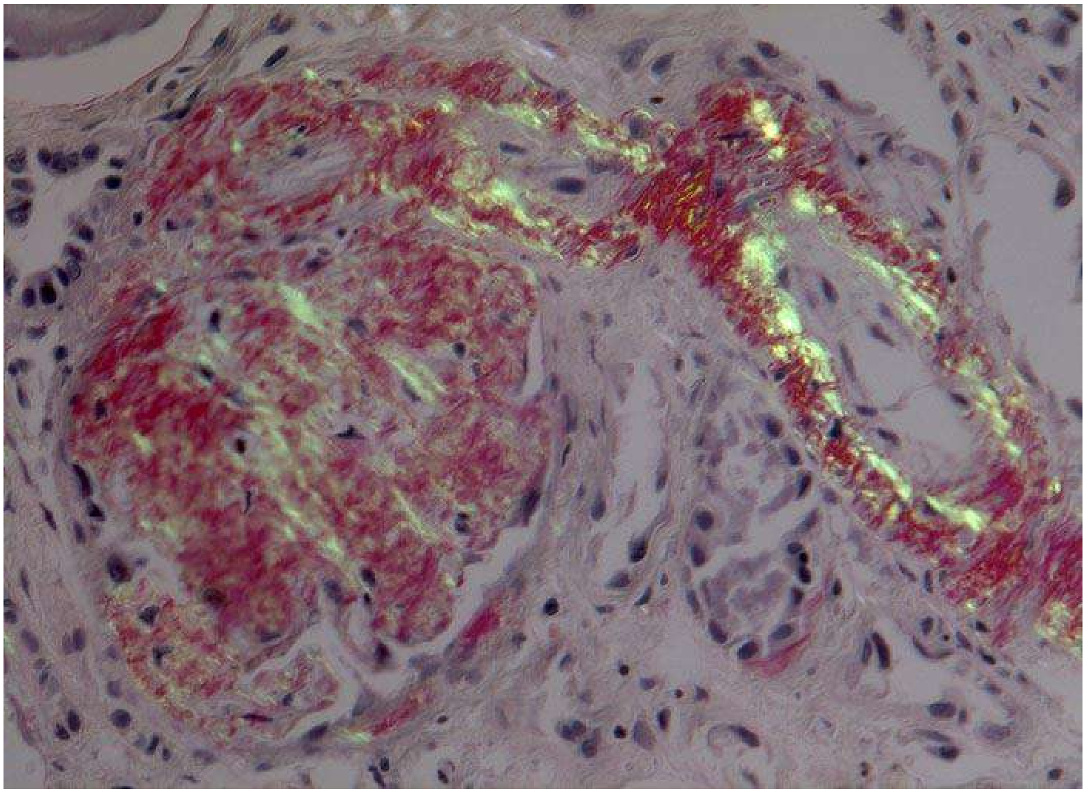
Beta-2 microglobulin amyloidosis
- precursor protein is beta-2 microglobulin, part of the major histocompatibility complex
- associated with patients on renal dialysis

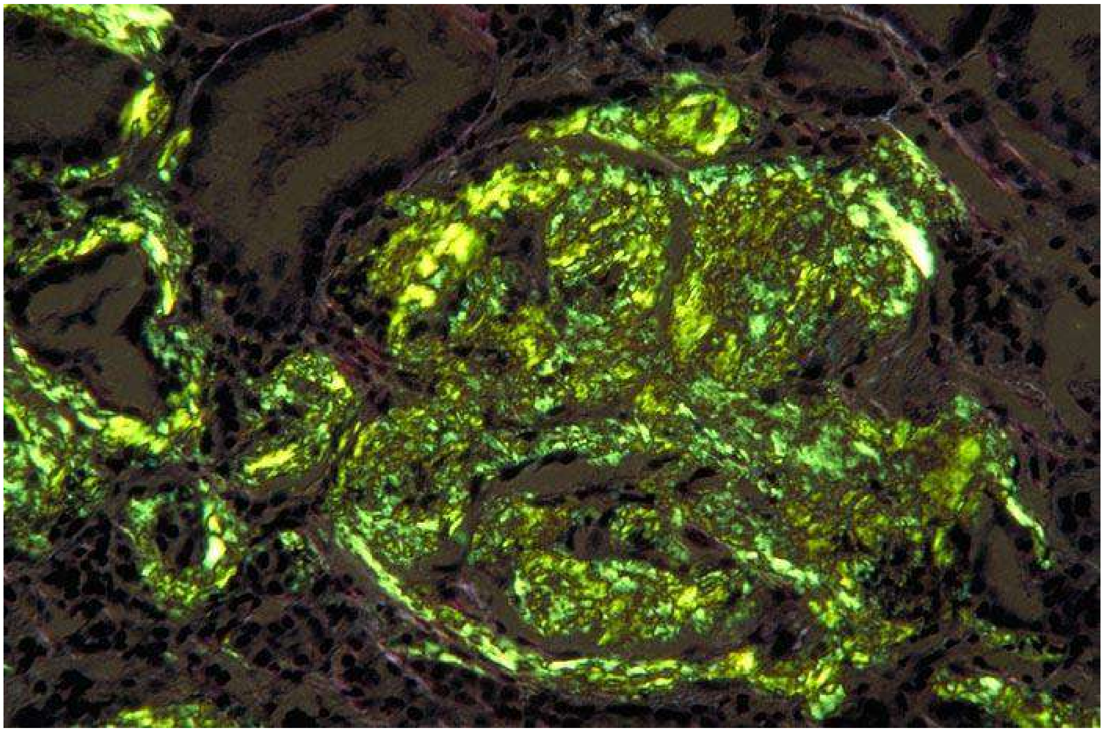
# AMYLOIDOSIS

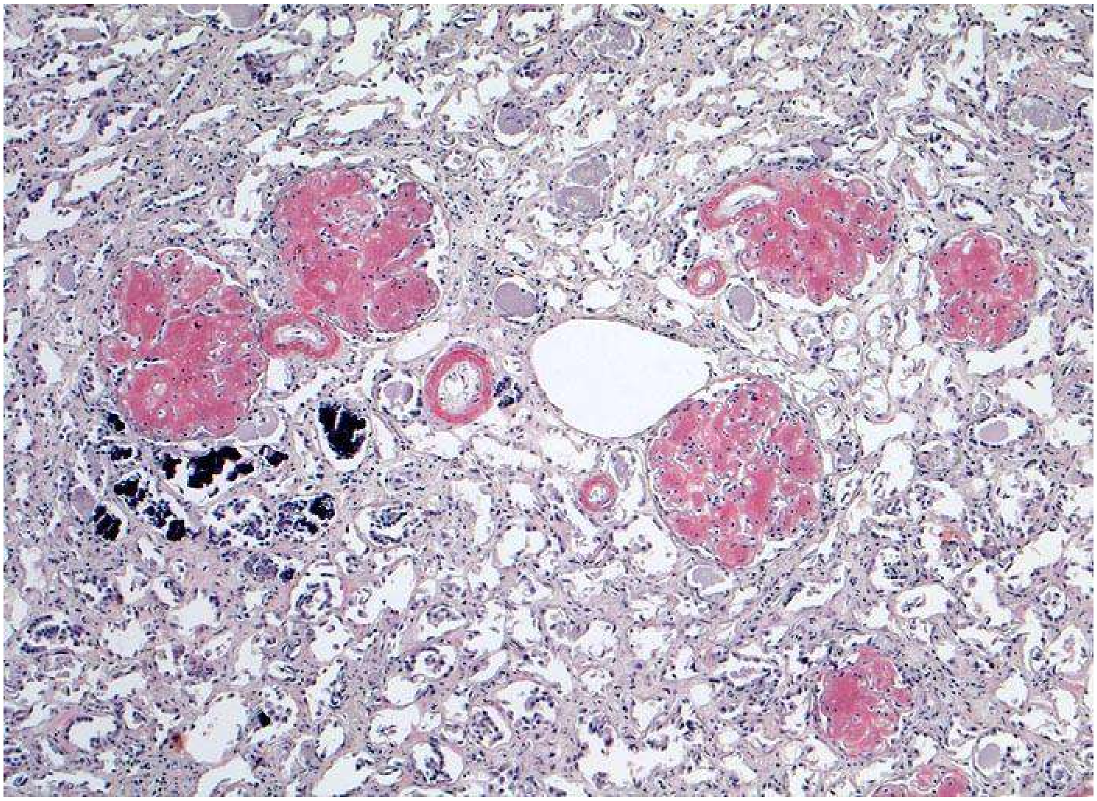
Overview
- amyloidosis is a term which describes the extracellular deposition of an insoluble fibrillar protein termed amyloid
- amyloid is derived from many different precursor proteins
- in addition to the fibrillar component, amyloid also contains a non-fibrillary protein called amyloid-P component, derived from the acute phase protein serum amyloid P
- other non-fibrillary components include apolipoprotein E and heparan sulphate proteoglycans
- the accumulation of amyloid fibrils leads to tissue/organ dysfunction

Classification
- systemic or localized
- further characterised by precursor protein (e.g. AL in myeloma - A for Amyloid, L for immunoglobulin Light chain fragments)

Diagnosis
- Congo red staining: apple-green birefringence
- serum amyloid precursor (SAP) scan
- biopsy of rectal tissue


Renal amyloid with congo red staining – apple-green birefringence


Renal amyloid with congo red staining – apple-green birefringence



Congo red staining. Amyloid deposites are seen in both the arteries/arterioles and within the glomerulus. The deposit of amyloid within the mesangium is not dissimilar to the nodular lesions seen in diabetic nephropathy

# SCROTAL PROBLEMS

**Epididymal cysts**

Epididymal cysts are the most common cause of scrotal swellings seen in primary care.

Features

- separate from the body of the testicle
- found posterior to the testicle

Associated conditions

- polycystic kidney disease
- cystic fibrosis
- von Hippel-Lindau syndrome

Diagnosis may be confirmed by ultrasound.

Management is usually supportive but surgical removal or sclerotherapy may be attempted for larger or symptomatic cysts.

**Hydrocele**

A hydrocele describes the accumulation of fluid within the tunica vaginalis. They can be divided into communicating and non-communicating:

- communicating: caused by patency of the processus vaginalis allowing peritoneal fluid to drain down into the scrotum. Communicating hydroceles are common in newborn males (clinically apparent in 5-10%) and usually resolve within the first few months of life
- non-communicating: caused by excessive fluid production within the tunica vaginalis

Hydroceles may develop secondary to:

- epididymo-orchitis
- testicular torsion
- testicular tumours

Features

- soft, non-tender swelling of the hemi-scrotum. Usually anterior to and below the testicle
- the swelling is confined to the scrotum, you can get 'above' the mass on examination
- transilluminates with a pen torch
- the testis may be difficult to palpate if the hydrocele is large

Diagnosis may be clinical but ultrasound is required if there is any doubt about the diagnosis or if the underlying testis cannot be palpated.

Management

- infantile hydroceles are generally repaired if they do not resolve spontaneously by the age of 1-2 years

- in adults a conservative approach may be taken depending on the severity of the presentation. Further investigation (e.g. ultrasound) is usually warranted however to exclude any underlying cause such as a tumour

**Varicocele**

A varicocele is an abnormal enlargement of the testicular veins. They are usually asymptomatic but may be important as they are associated with infertility.

Varicoceles are much more common on the left side (> 80%). Features:
- classically described as a 'bag of worms'
- subfertility

Diagnosis
- ultrasound with Doppler studies

Management
- usually conservative
- occasionally surgery is required if the patient is troubled by pain. There is ongoing debate regarding the effectiveness of surgery to treat infertility

# TESTICULAR CANCER

Testicular cancer is the most common malignancy in men aged 20-30 years. Around 95% of cases of testicular cancer are germ-cell tumours. Germ cell tumours may essentially be divided into:
- seminomas
- non-seminomas: including embryonal, yolk sac, teratoma and choriocarcinoma

Non-germ cell tumours include Leydig cell tumours and sarcomas.

The peak incidence for teratomas is 25 years and seminomas is 35 years. Risk factors include:
- infertility (increases risk by a factor of 3)
- cryptorchidism
- family history
- Klinefelter's syndrome
- mumps orchitis

Features
- a painless lump is the most common presenting symptom
- pain may also be present in a minority of men
- other possible features include hydrocele, gynaecomastia
- AFP is elevated in around 60% of germ cell tumours

- LDH is elevated in around 40% of germ cell tumours
- seminomas: hCG may be elevated in around 20%

Diagnosis
- ultrasound is first-line

Management
- treatment depends on whether the tumour is a seminoma or a non-seminoma
- orchidectomy
- chemotherapy and radiotherapy may be given depending on staging and tumour type

Prognosis is generally excellent
- 5 year survival for seminomas is around 95% if Stage I
- 5 year survival for teratomas is around 85% if Stage I

# BENIGN PROSTATIC HYPERPLASIA

Benign prostatic hyperplasia (BPH) is a common condition seen in older men.

Risk factors
- age: around 50% of 50-year-old men will have evidence of BPH and 30% will have symptoms. Around 80% of 80-year-old men have evidence of BPH
- ethnicity: black > white > Asian

BPH typically presents with lower urinary tract symptoms (LUTS), which may be categorised into:
- voiding symptoms (obstructive): weak or intermittent urinary flow, straining, hesitancy, terminal dribbling and incomplete emptying
- storage symptoms (irritative) urgency, frequency, urgency incontinence and nocturia
- post-micturition: dribbling
- complications: urinary tract infection, retention, obstructive uropathy

Management options
- watchful waiting
- medication: alpha-1 antagonists, 5 alpha-reductase inhibitors. The use of combination therapy was supported by the Medical Therapy Of Prostatic Symptoms (MTOPS) trial
- surgery: transurethral resection of prostate (TURP)

Alpha-1 antagonists e.g. tamsulosin, alfuzosin
- decrease smooth muscle tone (prostate and bladder)
- considered first-line, improve symptoms in around 70% of men
- adverse effects: dizziness, postural hypotension, dry mouth, depression

5 alpha-reductase inhibitors e.g. finasteride
- block the conversion of testosterone to dihydrotestosterone (DHT), which is known to induce BPH
- unlike alpha-1 antagonists causes a reduction in prostate volume and hence may slow disease progression. This however takes time and symptoms may not improve for 6 months. They may also decrease PSA concentrations by up to 50%
- adverse effects: erectile dysfunction, reduced libido, ejaculation problems, gynaecomastia

# PROSTATE CANCER: PSA TESTING

Prostate specific antigen (PSA) is a serine protease enzyme produced by normal and malignant prostate epithelial cells. It has become an important tumour marker but much controversy still exists regarding its usefulness as a screening tool.

The NHS Prostate Cancer Risk Management Programme (PCRMP) has published updated guidelines in 2009 on how to handle requests for PSA testing in asymptomatic men. A recent European trial (ERSPC) showed a statistically significant reduction in the rate of death prostate cancer by 20% in men aged 55 to 69 years but this was associated with a high risk of over-diagnosis and over-treatment. Having reviewed this and other data the National Screening Committee have decided not to introduce a prostate cancer screening programme yet but rather allow men to make an informed choice.

Age-adjusted upper limits for PSA were recommended by the PCRMP:

| Age | PSA level (ng/ml) |
|---|---|
| 50-59 years | 3.0 |
| 60-69 years | 4.0 |
| > 70 years | 5.0 |

However, NICE Clinical Knowledge Summaries currently suggest a different cut-off:

- men aged 50-69 years should be referred if the PSA is >= 3.0 ng/ml OR there is an abnormal DRE
- note this is a lower threshold than the PCRMP 60-69 years limits recommended above

PSA levels may also be raised by*:

- benign prostatic hyperplasia (BPH)
- prostatitis and urinary tract infection (NICE recommend to postpone the PSA test for at least 1 month after treatment)
- ejaculation (ideally not in the previous 48 hours)
- vigorous exercise (ideally not in the previous 48 hours)
- urinary retention
- instrumentation of the urinary tract

Poor specificity and sensitivity

- around 33% of men with a PSA of 4-10 ng/ml will be found to have prostate cancer. With a PSA of 10-20 ng/ml this rises to 60% of men
- around 20% with prostate cancer have a normal PSA
- various methods are used to try and add greater meaning to a PSA level including age-adjusted upper limits and monitoring change in PSA level with time (PSA velocity or PSA doubling time)

*whether digital rectal examination actually causes a rise in PSA levels is a matter of debate

# PROSTATE CANCER: MANAGEMENT

**Localised prostate cancer (T1/T2)**

Treatment depends on life expectancy and patient choice. Options include:

- conservative: active monitoring & watchful waiting

- radical prostatectomy
- radiotherapy: external beam and brachytherapy

**Localised advanced prostate cancer (T3/T4)**

Options include:

- hormonal therapy: see below
- radical prostatectomy: erectile dysfunction is a common complication
- radiotherapy: external beam and brachytherapy. Patients are at increased risk of bladder, colon, and rectal cancer following radiotherapy for prostate cancer

**Metastatic prostate cancer disease - hormonal therapy**

Synthetic GnRH agonist

  - e.g. Goserelin (Zoladex)
  - cover initially with anti-androgen to prevent rise in testosterone

Anti-androgen

- cyproterone acetate prevents DHT binding from intracytoplasmic protein complexes

Orchidectomy

# LOWER URINARY TRACT SYMPTOMS IN MEN

Lower urinary tract symptoms (LUTS) in men are very common and are present in the majority of men aged > 50 years. They are most commonly secondary to benign prostatic hyperplasia but other causes should be considered including prostate cancer.

It is useful to classify the symptoms into 3 broad groups.

| Voiding | Storage | Post-micturition |
|---|---|---|
| Hesitancy<br>Poor or intermittent stream<br>Straining<br>Incomplete emptying<br>Terminal dribbling | Urgency<br>Frequency<br>Nocturia<br>Urinary incontinence | Post-micturition dribbling<br>Sensation of incomplete emptying |

Examination

- urinalysis: exclude infection, check for haematuria
- digital rectal examination: size and consistency of prostate
- a PSA test may be indicated, but the patient should be properly counselled first

It is useful to get the patient to complete the following to guide management:

- urinary frequency-volume chart: distinguish between urinary frequency, polyuria, nocturia, and nocturnal polyuria.
- International Prostate Symptom Score (IPSS): assess the impact on the patient's life. This classifies the symptoms as mild, moderate or severe

**Management**

- Predominately voiding symptoms
- conservative measures include: pelvic floor muscle training, bladder training, prudent fluid intake and containment products
- if 'moderate' or 'severe' symptoms offer an alpha-blocker
- if the prostate is enlarged and the patient is 'considered at high risk of progression' then a 5-alpha reductase inhibitor should be offered
- if the patient has an enlarged prostate and 'moderate' or 'severe' symptoms offer both an alpha-blocker and 5-alpha reductase inhibitor
- if there are mixed symptoms of voiding and storage not responding to an alpha blocker then a antimuscarinic (anticholinergic) drug may be added

Predominately overactive bladder

- conservative measures include moderating fluid intake
- bladder retraining should be offered
- antimuscarinic drugs should be offered if symptoms persist. NICE recommend oxybutynin (immediate release), tolterodine (immediate release), or darifenacin (once daily preparation)
- mirabegron may be considered if first-line drugs fail

Nocturia

- advise about moderating fluid intake at night
- furosemide 40mg in late afternoon may be considered
- desmopressin may also be helpful

# EPIDIDYMO-ORCHITIS

Epididymo-orchitis describes an infection of the epididymis +/- testes resulting in pain and swelling. It is most commonly caused by local spread of infections from the genital tract (such as Chlamydia trachomatis and Neisseria gonorrhoeae) or the bladder.

**The most important differential diagnosis is testicular torsion. This needs to be excluded urgently to prevent ischaemia of the testicle.**

Features

- unilateral testicular pain and swelling
- urethral discharge may be present, but urethritis is often asymptomatic
- factors suggesting testicular torsion include patients < 20 years, severe pain and an acute onset

Management

- the British Association for Sexual Health and HIV (BASHH) produced guidelines in 2010
- if the organism is unknown BASHH recommend: ceftriaxone 500mg intramuscularly single dose, plus doxycycline 100mg by mouth twice daily for 10-14 days
- further investigations following treatment are recommended to exclude any underlying structural abnormalities

# CHRONIC PYELONEPHRITIS

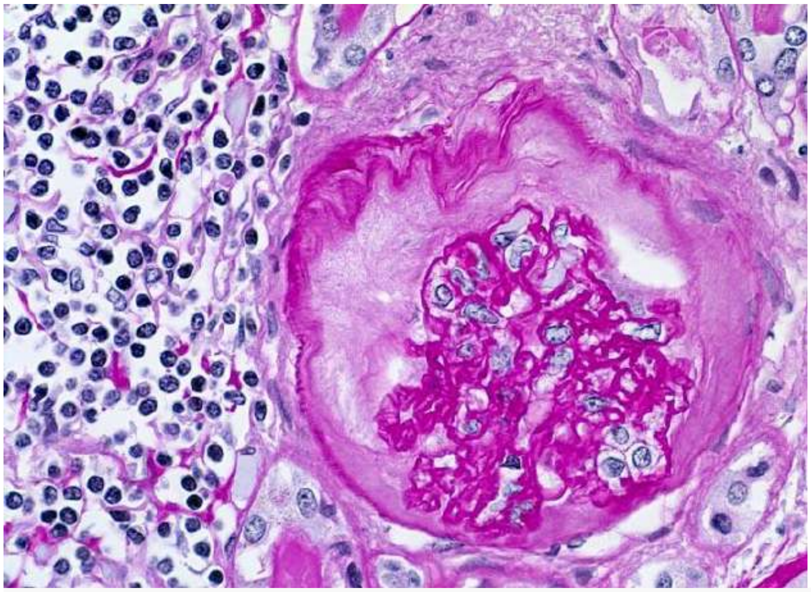
Chronic pyelonephritis is a form of chronic kidney disease caused by recurrent infections. This results in scarring of the renal parenchyma and impaired function. Chronic pyelonephritis accounts for around 15% of end-stage renal disease.

Predisposing factors

- vesicoureteral reflux in children
- obstruction e.g. recurrent renal stones

Key exam features

- blunted calyx
- corticomedullary scarring with atrophy of tubules
- eosinophilic casts in the tubules



Lymphocytic infiltrate with collapsed glomeruli and thickened Bowman's capsule.

## XANTHOGRANULOMATOUS PYELONEPHRITIS

Xanthogranulomatous pyelonephritis is a rare chronic granulomatous disease resulting in a non-functioning kidney. Chronic/subacute infection by organisms such as Proteus mirabilis predispose to renal stones including staghorn calculi. Foamy (lipid laden) macrophages are typically seen.

## REFLUX NEPHROPATHY

Overview

- term used to chronic pyelonephritis secondary to vesico-uretic reflux
- commonest cause of chronic pyelonephritis
- scarring usually occurs in first 5 years
- strong genetic disposition
- renal scar may produce increased quantities of renin causing hypertension

Diagnosis

- micturating cystography

# RENAL STONES: RISK FACTORS

Risk factors
- dehydration
- hypercalciuria, hyperparathyroidism, hypercalcaemia
- cystinuria
- high dietary oxalate
- renal tubular acidosis
- medullary sponge kidney, polycystic kidney disease
- beryllium or cadmium exposure

Risk factors for urate stones
- gout
- ileostomy: loss of bicarbonate and fluid results in acidic urine, causing the precipitation of uric acid

Drug causes
- drugs that promote calcium stones: loop diuretics, steroids, acetazolamide, theophylline
- thiazides can prevent calcium stones (increase distal tubular calcium resorption)

# CYSTINURIA

Cystinuria is an autosomal recessive disorder characterised by the formation of recurrent renal stones. It is due to a defect in the membrane transport of cystine, ornithine, lysine, arginine (mnemonic = COLA)

Genetics
- chromosome 2: SLC3A1 gene, chromosome 19: SLC7A9

Features
- recurrent renal stones
- are classically yellow and crystalline, appearing semi-opaque on x-ray

Diagnosis
- cyanide-nitroprusside test

Management
- hydration
- D-penicillamine
- urinary alkalinization

# RENAL STONES: IMAGING

The table below summarises the appearance of different types of renal stone on x-ray

| Type | Frequency | Radiograph appearance |
|---|---|---|
| Calcium oxalate | 40% | Opaque |
| Mixed calcium oxalate/phosphate stones | 25% | Opaque |
| Triple phosphate stones* | 10% | Opaque |
| Calcium phosphate | 10% | Opaque |
| Urate stones | 5-10% | Radio-lucent |
| Cystine stones | 1% | Semi-opaque, 'ground-glass' appearance |
| Xanthine stones | <1% | Radio-lucent |

*stag-horn calculi involve the renal pelvis and extend into at least 2 calyces. They develop in alkaline urine and are composed of struvite (ammonium magnesium phosphate, triple phosphate). Ureaplasma urealyticum and Proteus infections predispose to their formation

# RENAL STONES: MANAGEMENT

The British Association of Urological Surgeons (BAUS) published guidelines in 2018 on the management of acute ureteric/renal colic.

**Initial management of renal colic**

Medication

- the BAUS recommend an NSAID as the analgesia of choice for renal colic
- whilst diclofenac has been traditionally used the increased risk of cardiovascular events with certain NSAIDs (e.g. diclofenac, ibuprofen) should be considered when prescribing
- the CKS guidelines suggest for patients who require admission: 'Administer a parenteral analgesic (such as intramuscular diclofenac) for rapid relief of severe pain'
- BAUS no longer endorse the use of alpha-adrenergic blockers to aid ureteric stone passage routinely. They do however acknowledge a recently published meta-analysis advocates the use of α-blockers for patients amenable to conservative management, with greatest benefit amongst those with larger stones

Initial investigations

- urine dipstick and culture
- serum creatinine and electrolytes: check renal function
- FBC / CRP: look for associated infection
- calcium/urate: look for underlying causes

- also: clotting if percutaneous intervention planned and blood cultures if pyrexial or other signs of sepsis

Imaging
- BAUS now recommend that non-contrast CT KUB should be performed on all patients, within 14 hours of admission
- if a patient has a fever, a solitary kidney or when the diagnosis is uncertain an immediate CT KUB should be performed. In the case of an uncertain diagnosis, this is to exclude other diagnoses such as ruptured abdominal aortic aneurysm
- CT KUB has a sensitivity of 97% for ureteric stones and a specificity of 95%
- ultrasound still has a role but given the wider availability of CT now and greater accurary it is no longer recommend first-line. The sensitivity of ultrasound for stones is around 45% and specificity is around 90%

**Management of renal stones**

Stones < 5 mm will usually pass spontaneously. Lithotripsy and nephrolithotomy may be for severe cases.

Most renal stones measuring less than 5mm in maximum diameter will typically pass within 4 weeks of symptom onset. More intensive and urgent treatment is indicated in the presence of ureteric obstruction, renal developmental abnormality such as horseshoe kidney and previous renal transplant. Ureteric obstruction due to stones together with infection is a surgical emergency and the system must be decompressed. Options include nephrostomy tube placement, insertion of ureteric catheters and ureteric stent placement.

In the non-emergency setting, the preferred options for treatment of stone disease include extra corporeal shock wave lithotripsy, percutaneous nephrolithotomy, ureteroscopy, open surgery remains an option for selected cases. However, minimally invasive options are the most popular first-line treatment.

Shockwave lithotripsy
- A shock wave is generated external to the patient, internally cavitation bubbles and mechanical stress lead to stone fragmentation. The passage of shock waves can result in the development of solid organ injury. Fragmentation of larger stones may result in the development of ureteric obstruction. The procedure is uncomfortable for patients and analgesia is required during the procedure and afterwards.

Ureteroscopy
- A ureteroscope is passed retrograde through the ureter and into the renal pelvis. It is indicated in individuals (e.g. pregnant females) where lithotripsy is contraindicated and in complex stone disease. In most cases a stent is left in situ for 4 weeks after the procedure.

Percutaneous nephrolithotomy

- In this procedure, access is gained to the renal collecting system. Once access is achieved, intra corporeal lithotripsy or stone fragmentation is performed and stone fragments removed.

**Therapeutic selection**

| Disease | Option |
|---|---|
| Stone burden of less than 2cm in aggregate | Lithotripsy |
| Stone burden of less than 2cm in pregnant females | Ureteroscopy |
| Complex renal calculi and staghorn calculi | Percutaneous nephrolithotomy |
| Ureteric calculi less than 5mm | Manage expectantly |

**Prevention of renal stones**

Calcium stones may be due to hypercalciuria, which is found in up to 5-10% of the general population.

- high fluid intake
- low animal protein, low salt diet (a low calcium diet has not been shown to be superior to a normocalcaemic diet)
- thiazides diuretics (increase distal tubular calcium resorption)

Oxalate stones

- cholestyramine reduces urinary oxalate secretion
- pyridoxine reduces urinary oxalate secretion

Uric acid stones

- allopurinol
- urinary alkalinization e.g. oral bicarbonate

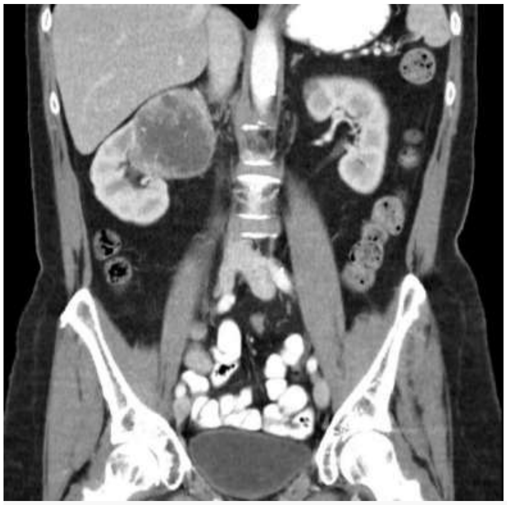
# RENAL CELL CANCER

Renal cell cancer is also known as hypernephroma and accounts for 85% of primary renal neoplasms. It arises from proximal renal tubular epithelium. The most common histological subtype is clear cell (75 to 85 percent of tumours).

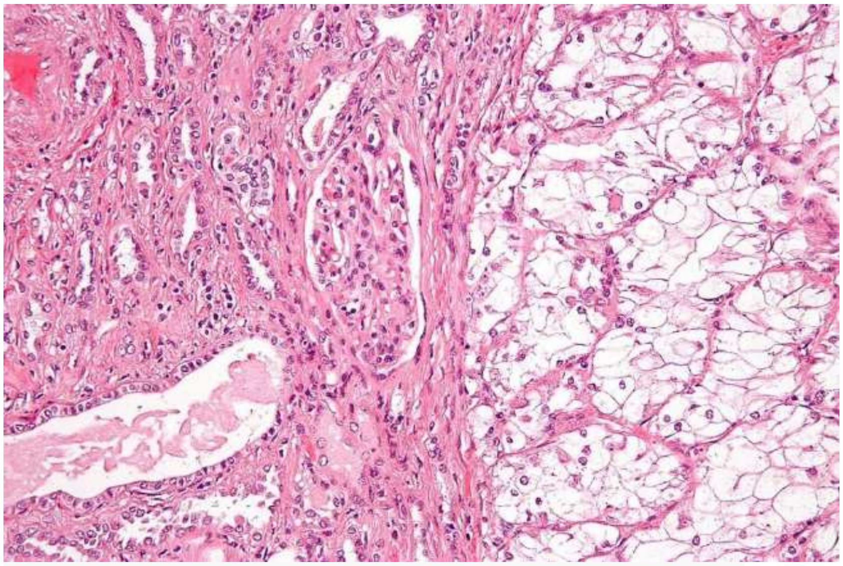
Associations*
- more common in middle-aged men
- smoking
- von Hippel-Lindau syndrome
- tuberous sclerosis

Features
- classical triad: haematuria, loin pain, abdominal mass
- pyrexia of unknown origin
- left varicocele (due to occlusion of left testicular vein)
- endocrine effects: may secrete erythropoietin (polycythaemia), parathyroid hormone (hypercalcaemia), renin, ACTH
- 25% have metastases at presentation
- paraneoplastic hepatic dysfunction syndrome. Also known as Stauffer syndrome. Typically presents as cholestasis/hepatosplenomegaly. It is thought to be secondary to increased levels of IL-6

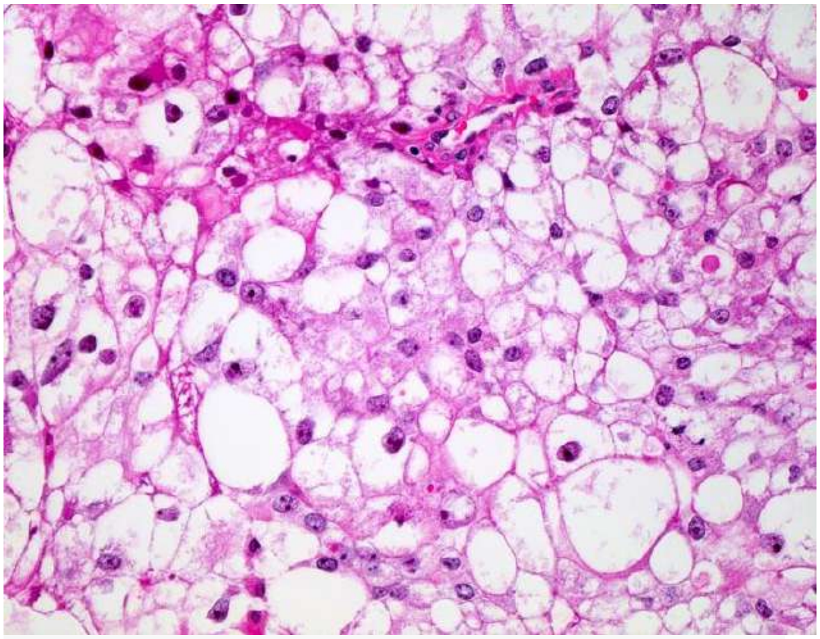
Management
- for confined disease a partial or total nephrectomy depending on the tumour size
- alpha-interferon and interleukin-2 have been used to reduce tumour size and also treat patients with metatases
- receptor tyrosine kinase inhibitors (e.g. sorafenib, sunitinib) have been shown to have superior efficacy compared to interferon-alpha



Coronal CT scan of a middle-aged woman with renal cell cancer. Note the heterogeneously enhancing mass at the upper pole of the right kidney



Left: normal kidney. Right: 'clear-cell' pattern of renal cell carcinoma



'Clear-cell' pattern of renal cell carcinoma - clear cytoplasm, small nuclei

*incidence of renal cell cancer is only slightly increased in patients with autosomal dominant polycystic kidney disease

## BLADDER CANCER: RISK FACTORS

Risk factors for transitional cell carcinoma of the bladder include:

- Smoking
- Exposure to aniline dyes in the printing and textile industry: examples are 2-naphthylamine and benzidine
- Rubber manufacture

- Cyclophosphamide

Risk factors for squamous cell carcinoma of the bladder include:
- Schistosomiasis
- Smoking

## RETROPERITONEAL FIBROSIS

Lower back/flank pain is the most common presenting feature. Fever and lower limb oedema is also seen in some patients.

Associations
- Riedel's thyroiditis
- previous radiotherapy
- sarcoidosis
- inflammatory abdominal aortic aneurysm
- drugs: methysergide

## FANCONI SYNDROME

Fanconi syndrome describes a generalised reabsorptive disorder of renal tubular transport in the proximal convoluted tubule resulting in:
- type 2 (proximal) renal tubular acidosis
- polyuria
- aminoaciduria
- glycosuria
- phosphaturia
- osteomalacia

Causes
- cystinosis (most common cause in children)
- Sjogren's syndrome
- multiple myeloma
- nephrotic syndrome
- Wilson's disease

## ALPORT'S SYNDROME

Alport's syndrome is usually inherited in an X-linked dominant pattern*. It is due to a defect in the gene which codes for type IV collagen resulting in an abnormal glomerular-basement membrane (GBM). The disease is more severe in males with females rarely developing renal failure.

A favourite question is an Alport's patient with a failing renal transplant. This may be caused by the presence of anti-GBM antibodies leading to a Goodpasture's syndrome like picture.

Alport's syndrome usually presents in childhood. The following features may be seen:

- microscopic haematuria
- progressive renal failure
- bilateral sensorineural deafness
- lenticonus: protrusion of the lens surface into the anterior chamber
- retinitis pigmentosa
- renal biopsy: splitting of lamina densa seen on electron microscopy

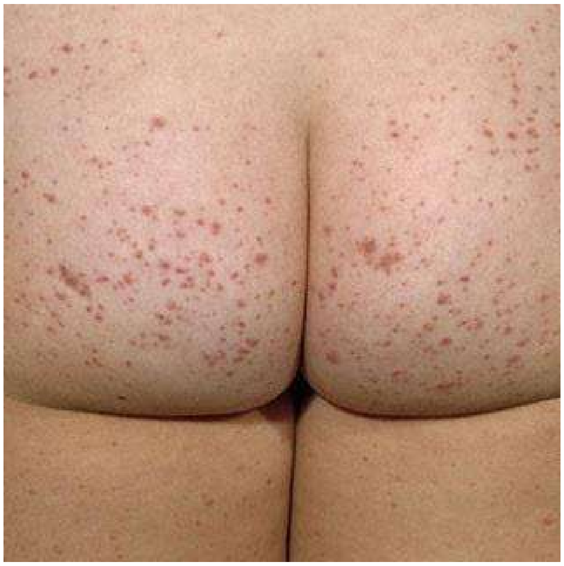
Diagnosis
- molecular genetic testing
- renal biopsy
  - electron microscopy: characteristic finding is of the longitudinal splitting of the lamina densa of the glomerular basement membrane, resulting in a 'basket-weave' appearance

*in around 85% of cases - 10-15% of cases are inherited in an autosomal recessive fashion with rare autosomal dominant variants existing

# HENOCH-SCHONLEIN PURPURA

Henoch-Schonlein purpura (HSP) is an IgA mediated small vessel vasculitis. There is a degree of overlap with IgA nephropathy (Berger's disease). HSP is usually seen in children following an infection.

Features
- palpable purpuric rash (with localized oedema) over buttocks and extensor surfaces of arms and legs
- abdominal pain
- polyarthritis
- features of IgA nephropathy may occur e.g. haematuria, renal failure

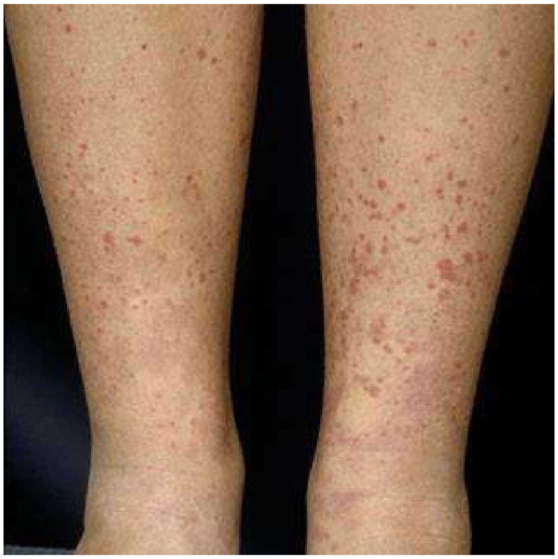


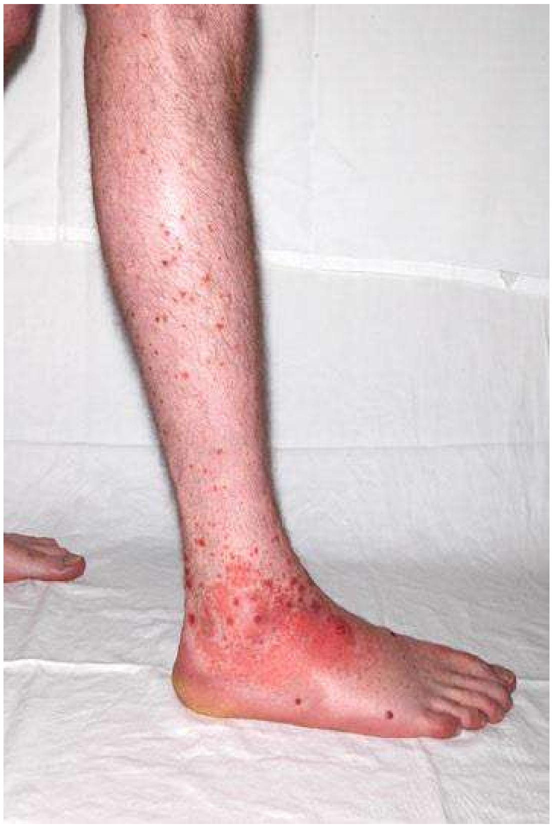
Treatment

- analgesia for arthralgia
- treatment of nephropathy is generally supportive. There is inconsistent evidence for the use of steroids and immunosuppressants

Prognosis

- usually excellent, HSP is a self-limiting condition, especially in children without renal involvement
- around 1/3rd of patients have a relapse





# THIN BASEMENT MEMBRANE DISEASE

An inherited disorder of type IV collagen that causes thinning of the basement membrane. It may affect up to 5% of the population and about 30% patients report a family history of haematuria. Diagnosis is usually based on the history of persistent haematuria, normal kidney function and family history of haematuria without kidney failure. It is generally a benign disorder and biopsy is rarely indicated.

# DIABETIC NEPHROPATHY: STAGES

Diabetic nephropathy may be classified as occurring in five stages*:

Stage 1
- hyperfiltration: increase in GFR
- may be reversible

Stage 2 (silent or latent phase)
- most patients do not develop microalbuminuria for 10 years
- GFR remains elevated

Stage 3 (incipient nephropathy)
- microalbuminuria (albumin excretion of 30 - 300 mg/day, dipstick negative)

Stage 4 (overt nephropathy)
- persistent proteinuria (albumin excretion > 300 mg/day, dipstick positive)
- hypertension is present in most patients
- histology shows diffuse glomerulosclerosis and focal glomerulosclerosis (Kimmelstiel-Wilson nodules)

Stage 5
- end-stage renal disease, GFR typically < 10ml/min
- renal replacement therapy needed

The timeline given here is for type 1 diabetics. Patients with type 2 diabetes mellitus (T2DM) progress through similar stages but in a different timescale - some T2DM patients may progress quickly to the later stages

# RENAL VASCULAR DISEASE

Renal vascular disease is most commonly due to atherosclerosis (> 95% of patients). It is associated with risk factors such as smoking and hypertension that cause atheroma elsewhere in the body. It may present as hypertension, chronic renal failure or 'flash' pulmonary oedema. In younger patients however fibromuscular dysplasia (FMD) needs to be considered. FMD is more common in young women and characteristically has a 'string of beads' appearance on angiography. Patients respond well to balloon angioplasty

Investigation
- MR angiography is now the investigation of choice
- CT angiography

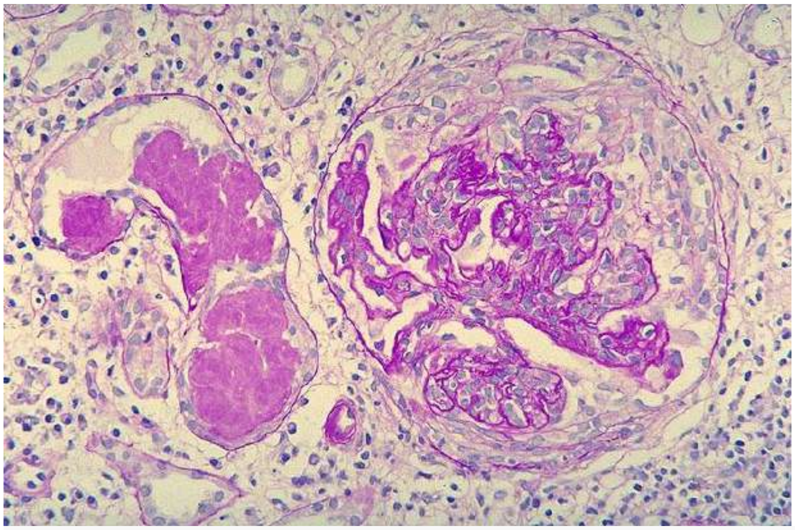
- conventional renal angiography is less commonly performed used nowadays, but may still have a role when planning surgery

# SYSTEMIC LUPUS ERYTHEMATOSUS: RENAL COMPLICATIONS

Lupus nephritis is a severe manifestation of systemic lupus erythematosus (SLE) that can result in end-stage renal disease. SLE patients should be monitored by performing urinalysis at regular check-up appointments to rule out proteinuria.

WHO classification
- class I: normal kidney
- class II: mesangial glomerulonephritis
- class III: focal (and segmental) proliferative glomerulonephritis
- class IV: diffuse proliferative glomerulonephritis
- class V: diffuse membranous glomerulonephritis
- class VI: sclerosing glomerulonephritis

Class IV (diffuse proliferative glomerulonephritis) is the most common and severe form. Renal biopsy characteristically shows the following findings:
- glomeruli shows endothelial and mesangial proliferation, 'wire-loop' appearance
- if severe, the capillary wall may be thickened secondary to immune complex deposition
- electron microscopy shows subendothelial immune complex deposits
- granular appearance on immunofluorescence



Diffuse proliferative SLE. Proliferation of endothelial and mesangial cells. The thickening of the capillary wall results in a 'wire-loop' appearance. Some crescents are present.

Management
- treat hypertension
- corticosteroids if clinical evidence of disease

- immunosuppressants e.g. azathioprine/cyclophosphamide

# HIV: RENAL INVOLVEMENT

Renal involvement in HIV patients may occur as a consequence of treatment or the virus itself. Protease inhibitors such as indinavir can precipitate intratubular crystal obstruction.

HIV-associated nephropathy (HIVAN) accounts for up to 10% of end-stage renal failure cases in the United States. Antiretroviral therapy has been shown to alter the course of the disease. There are five key features of HIVAN:

- massive proteinuria resulting in nephrotic syndrome
- normal or large kidneys
- focal segmental glomerulosclerosis with focal or global capillary collapse on renal biopsy
- elevated urea and creatinine
- normotension

# DIABETES INSIPIDUS

Diabetes insipidus (DI) is a condition characterised by either a deficiency of antidiuretic hormone, ADH, (cranial DI) or an insensitivity to antidiuretic hormone (nephrogenic DI).

Causes of cranial DI

- idiopathic
- post head injury
- pituitary surgery
- craniopharyngiomas
- histiocytosis X
- DIDMOAD is the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as Wolfram's syndrome)
- haemochromatosis

Causes of nephrogenic DI

- genetic: the more common form affects the vasopression (ADH) receptor, the less common form results from a mutation in the gene that encodes the aquaporin 2 channel
- electrolytes: hypercalcaemia, hypokalaemia
- drugs: demeclocycline, lithium
- tubulo-interstitial disease: obstruction, sickle-cell, pyelonephritis

Features

- polyuria
- polydipsia

Investigation

- high plasma osmolality, low urine osmolality
- a urine osmolality of >700 mOsm/kg excludes diabetes insipidus
- water deprivation test

Management

- nephrogenic diabetes insipidus: thiazides, low salt/protein diet

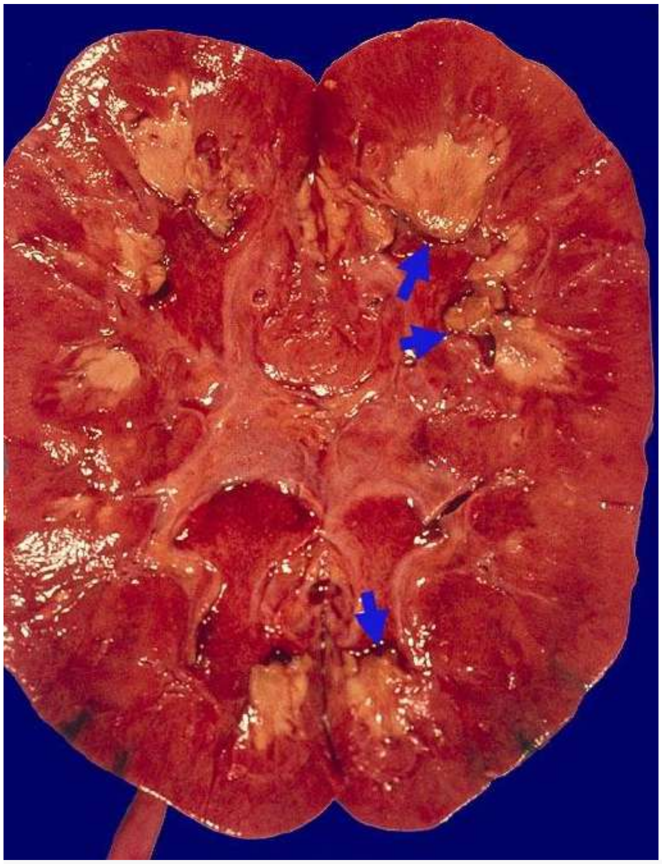
- central diabetes insipidus can be treated with desmopressin

# RENAL PAPILLARY NECROSIS

Renal papillary necrosis describes the coagulative necrosis of the renal papillae due to a variety of causes.

Causes
- severe acute pyelonephritis
- diabetic nephropathy
- obstructive nephropathy
- analgesic nephropathy
- phenacetin was the classic cause but this has now been withdrawn
- NSAIDs
- sickle cell anaemia

Features
- visible haematuria
- loin pain
- proteinuria



Renal papillary necrosis secondary to acute pyelonephritis. Note the pale areas highlighted by the blue arrows

# PAPILLARY NECROSIS

Causes

- chronic analgesia use
- sickle cell disease
- TB
- acute pyelonephritis
- diabetes mellitus

Features

- fever, loin pain, haematuria
- IVU - papillary necrosis with renal scarring - 'cup & spill'

# FIBROMUSCULAR DYSPLASIA

Renal artery stenosis secondary to atherosclerosis accounts for around 90% of renal vascular disease, with fibromuscular dysplasia being the most common cause of the remaining 10%.

Epidemiology

- 90% of patients are female

Features

- hypertension
- chronic kidney disease or more acute renal failure e.g. secondary to ACE-inhibitor initiation
- 'flash' pulmonary oedema

# ARTERIOVENOUS FISTULAS

Arteriovenous fistulas are direct connections between arteries and veins. They may occur pathologically but are generally formed surgically to allow access for haemodialysis.

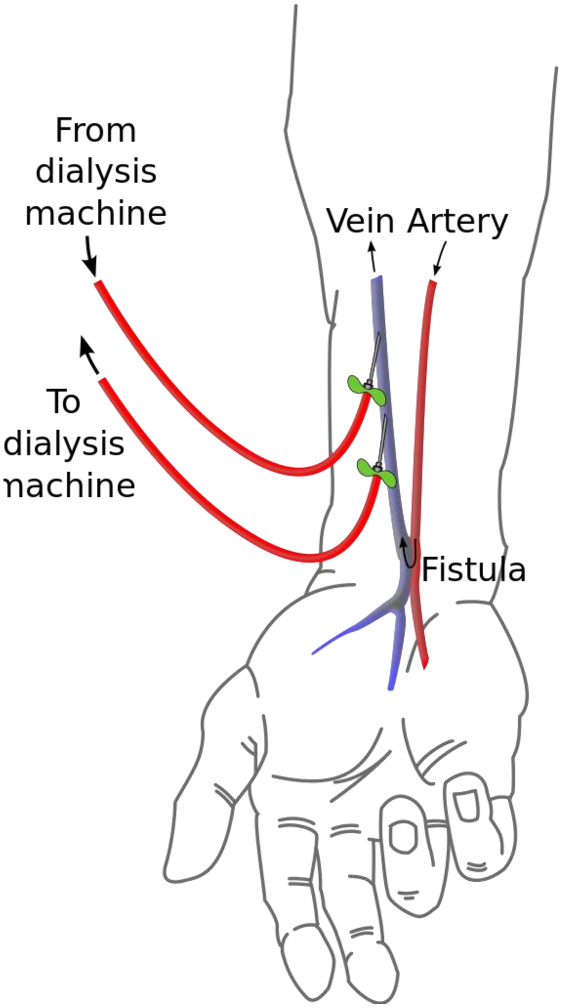
They are now regarded as the preferred method of access for haemodialysis due to the lower rates of complications.

The time taken for an arteriovenous fistula to develop is 6 to 8 weeks.

Potential complications include:

- infection
- thrombosis
- ○ may be detected by the absence of a bruit

- stenosis
    - may present with acute limb pain
- steal syndrome


From dialysis machine
To dialysis machine
Vein
Artery
Fistula

# METABOLIC ACIDOSIS

Metabolic acidosis is commonly classified according to the anion gap. This can be calculated by: (Na+ + K+) - (Cl- + HCO-3). If a question supplies the chloride level then this is often a clue that the anion gap should be calculated. The normal range = 10-18 mmol/L

Normal anion gap ( = hyperchloraemic metabolic acidosis)
- gastrointestinal bicarbonate loss: diarrhoea, ureterosigmoidostomy, fistula
- renal tubular acidosis
- drugs: e.g. acetazolamide
- ammonium chloride injection
- Addison's disease

Raised anion gap
- lactate: shock, sepsis, hypoxia
- ketones: diabetic ketoacidosis, alcohol
- urate: renal failure
- acid poisoning: salicylates, methanol

Metabolic acidosis secondary to high lactate levels may be subdivided into two types:
- lactic acidosis type A: sepsis, shock, hypoxia, burns
- lactic acidosis type B: metformin

# ANION GAP

The anion gap is calculated by:

(sodium + potassium) - (bicarbonate + chloride)

A normal anion gap is 8-14 mmol/L

It is useful to consider in patients with a metabolic acidosis:

Causes of a normal anion gap or hyperchloraemic metabolic acidosis
- gastrointestinal bicarbonate loss: diarrhoea, ureterosigmoidostomy, fistula
- renal tubular acidosis
- drugs: e.g. acetazolamide
- ammonium chloride injection
- Addison's disease

Causes of a raised anion gap metabolic acidosis

- lactate: shock, hypoxia
- ketones: diabetic ketoacidosis, alcohol
- urate: renal failure
- acid poisoning: salicylates, methanol
- 5-oxoproline: chronic paracetamol use

# HYPERKALAEMIA: MANAGEMENT

Untreated hyperkalaemia may cause life-threatening arrhythmias. Precipitating factors should be addressed (e.g. acute renal failure) and aggravating drugs stopped (e.g. ACE inhibitors). Management may be categorised by the aims of treatment

Stabilisation of the cardiac membrane

- intravenous calcium gluconate
    - does NOT lower serum potassium levels

Short-term shift in potassium from extracellular to intracellular fluid compartment

- combined insulin/dextrose infusion
- nebulised salbutamol

Removal of potassium from the body

- calcium resonium (orally or enema)
    - enemas are more effective than oral as potassium is secreted by the rectum
- loop diuretics
- dialysis
    - haemofiltration/haemodialysis should be considered for patients with AKI with persistent hyperkalaemia

# RENAL TRANSPLANT: HLA TYPING AND GRAFT FAILURE

The human leucocyte antigen (HLA) system is the name given to the major histocompatibility complex (MHC) in humans. It is coded for on chromosome 6.

Some basic points on the HLA system
- class 1 antigens include A, B and C. Class 2 antigens include DP,DQ and DR
- when HLA matching for a renal transplant the relative importance of the HLA antigens are as follows DR > B > A

Graft survival
- 1 year = 90%, 10 years = 60% for cadaveric transplants
- 1 year = 95%, 10 years = 70% for living-donor transplants

Post-op problems
- ATN of graft
- vascular thrombosis
- urine leakage
- UTI

Hyperacute rejection (minutes to hours)
- due to pre-existing antibodies against ABO or HLA antigens
- an example of a type II hypersensitivity reaction
- leads to widespread thrombosis of graft vessels → ischaemia and necrosis of the transplanted organ
- no treatment is possible and the graft must be removed

Acute graft failure (< 6 months)
- usually due to mismatched HLA. Cell-mediated (cytotoxic T cells)
- other causes include cytomegalovirus infection
- may be reversible with steroids and immunosuppressants

Causes of chronic graft failure (> 6 months)
- both antibody and cell mediated mechanisms cause fibrosis to the transplanted kidney (chronic allograft nephropathy)
- recurrence of original renal disease (MCGN > IgA > FSGS)

# RENAL TRANSPLANT: IMMUNOSUPPRESSION

Example regime
- initial: ciclosporin/tacrolimus with a monoclonal antibody

- maintenance: ciclosporin/tacrolimus with MMF or sirolimus
- add steroids if more than one steroid responsive acute rejection episode

Ciclosporin
- inhibits calcineurin, a phosphotase involved in T cell activation

Tacrolimus
- lower incidence of acute rejection compared to ciclosporin
- also less hypertension and hyperlipidaemia
- however, high incidence of impaired glucose tolerance and diabetes

Mycophenolate mofetil (MMF)
- blocks purine synthesis by inhibition of IMPDH
- therefore inhibits proliferation of B and T cells
- side-effects: GI and marrow suppression

Sirolimus (rapamycin)
- blocks T cell proliferation by blocking the IL-2 receptor
- can cause hyperlipidaemia

Monoclonal antibodies
- selective inhibitors of IL-2 receptor
- daclizumab
- basilximab

**Monitoring**
Patients on long-term immunosuppression for organ transplantation require regular monitoring for complications such as:

Cardiovascular disease - tacrolimus and ciclosporin can cause hypertension and hyperglycaemia. Tacrolimus can also cause hyperlipidaemia. Patients must be monitored for accelerated cardiovascular disease.

Renal failure - due to nephrotoxic effects of tacrolimus and ciclosporin/graft rejection/recurrence of original disease in transplanted kidney

Malignancy - patients should be educated about minimising sun exposure to reduce the risk of squamous cell carcinomas and basal cell carcinomas

# PERITONEAL DIALYSIS

Peritoneal dialysis (PD) is a form of renal replacement therapy. It is sometimes used as a stop-gap to haemodialysis or for younger patients who do not want to have to visit hospital three times a week.

The majority of patients do Continuous Ambulatory Peritoneal Dialysis (CAPD), which involves four 2-litre exchanges/day.

Complications
- peritonitis: coagulase-negative staphylococci such as Staphylococcus epidermidis is the most common cause. Staphylococcus aureus is another common cause
- sclerosing peritonitis

# PLASMA EXCHANGE

Indications for plasma exchange (also known as plasmapheresis)
- Guillain-Barre syndrome
- myasthenia gravis
- Goodpasture's syndrome
- ANCA positive vasculitis if rapidly progressive renal failure or pulmonary haemorrhage
- TTP/HUS
- cryoglobulinaemia
- hyperviscosity syndrome e.g. secondary to myeloma

Complications of plasma exchange
- hypocalcaemia: due to the presence of citrate used as an anticoagulant for the extracorporeal system
- metabolic alkalosis
- removal of systemic medications
- coagulation factor depletion
- immunoglobulin depletion

# NEPHROTOXICITY DUE TO CONTRAST MEDIA

Contrast media nephrotoxicity may be defined as a 25% increase in creatinine occurring within 3 days of the intravascular administration of contrast media.

Risk factors include
- known renal impairment (especially diabetic nephropathy)
- age > 70 years

- dehydration
- cardiac failure
- the use of nephrotoxic drugs such as NSAIDs

Contrast-induced nephropathy occurs 2 -5 days after administration.

Prevention

- the evidence base currently supports the use of intravenous 0.9% sodium chloride at a rate of 1 mL/kg/hour for 12 hours pre- and post- procedure. There is also evidence to support the use of isotonic sodium bicarbonate
- N-acetylcysteine has been given in the past but recent evidence suggests it is not effective*

* Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine. N Engl J Med. 2018;378(7):603

# FLUID THERAPY

The prescription of intravenous fluids is one of the most common tasks that junior doctors need to do.

In the 2013 guidelines NICE recommend the following requirements for maintenance fluids:

- 25-30 ml/kg/day of water and
- approximately 1 mmol/kg/day of potassium, sodium and chloride and
- approximately 50-100 g/day of glucose to limit starvation ketosis

So, for a 80kg patient, for a 24 hour period, this would translate to:

- 2 litres of water
- 80mmol potassium

For the first 24 hours NICE recommend the following::

*When prescribing for routine maintenance alone, consider using 25-30 ml/kg/day sodium chloride 0.18% in 4% glucose with 27 mmol/l potassium on day 1 (there are other regimens to achieve this).*

The amount of fluid patients require obviously varies according to their recent and past medical history. For example a patient who is post-op and is having significant losses from drains will require more fluid whereas a patient with heart failure should be given less fluid to avoid precipitating pulmonary oedema.

The table below shows the electrolyte concentrations (in millimoles/litre) of plasma and the most commonly used fluids:

| | $Na^+$ | $Cl^-$ | $K^+$ | $HCO3^-$ | Glucose |
|---|---|---|---|---|---|
| **Plasma** | 135-145 | 98-105 | 3.5-5 | 22-28 | - |
| **0.9% saline** | 154 | 154 | - | - | - |
| **5% glucose** | - | - | - | - | 50g |
| **0.18% saline with 4% glucose** | 30 | 30 | - | - | 40g |
| **Hartmann's solution** | 131 | 111 | 5 | 29 | - |

**Specific points**

0.9% saline

- if large volumes are used there is an increased risk of hyperchloraemic metabolic acidosis

Hartmann's

- contains potassium and therefore should not be used in patients with hyperkalaemia

# PASSMEDICINE NOTES

# HAEMATOLOGY & ONCOLOGY

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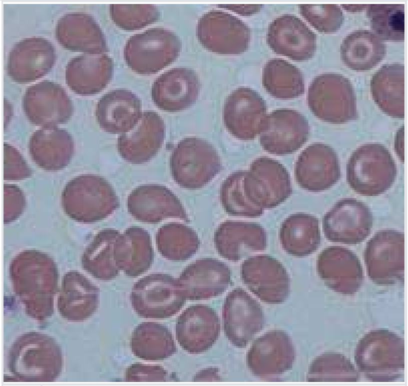
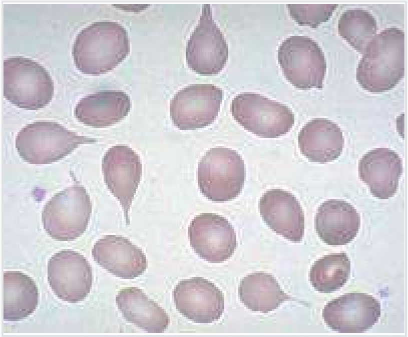
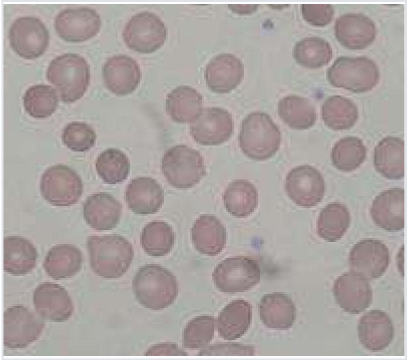
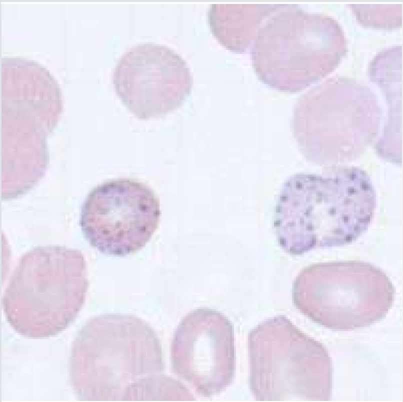
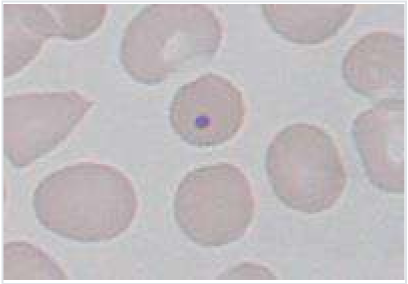
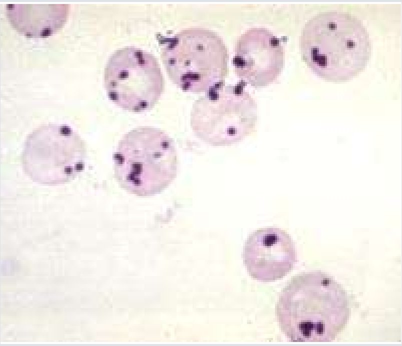
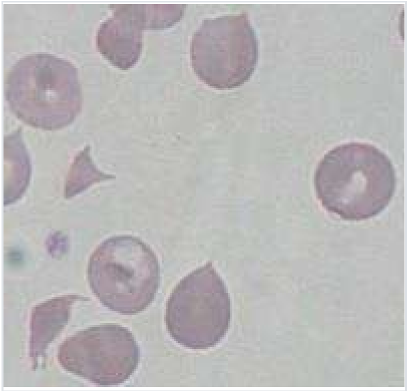
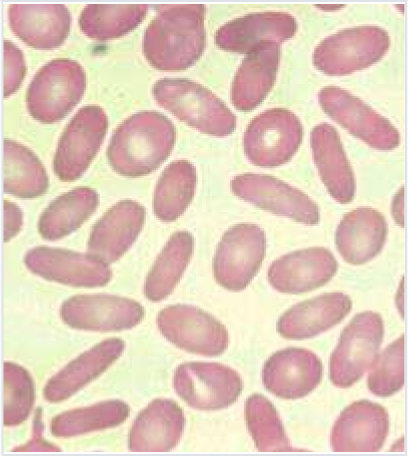
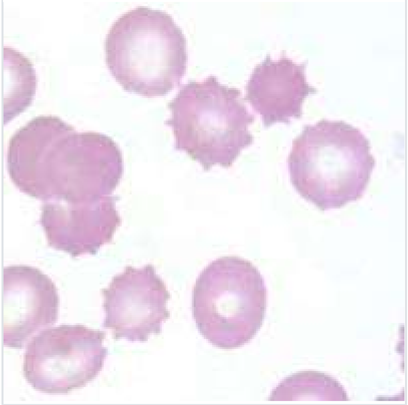
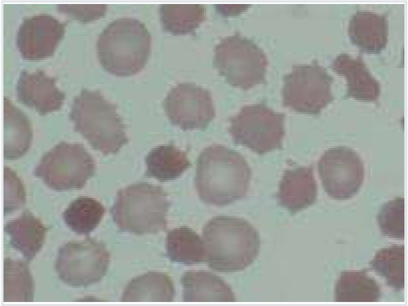
# BLOOD FILMS: PATHOLOGICAL CELL FORMS

## Pathological red cell forms

| Abnormality | Associated condition(s) | Appearance |
|---|---|---|
| Target cells | Sickle-cell/thalassaemia<br>Iron-deficiency anaemia<br>Hyposplenism<br>Liver disease |  |
| 'Tear-drop' poikilocytes | Myelofibrosis |  |
| Spherocytes | Hereditary spherocytosis<br>Autoimmune hemolytic anaemia |  |

| Abnormality | Associated condition(s) | Appearance |
|---|---|---|
| Basophilic stippling | Lead poisoning<br>Thalassaemia<br>Sideroblastic anaemia<br>Myelodysplasia |  |
| Howell-Jolly bodies | Hyposplenism |  |
| Heinz bodies | G6PD deficiency<br>Alpha-thalassaemia |  |
| Schistocytes ('helmet cells') | Intravascular haemolysis<br>Mechanical heart valve<br>Disseminated intravascular coagulation |  |

| Abnormality | Associated condition(s) | Appearance |
|---|---|---|
| 'Pencil' poikilocytes | Iron deficency anaemia |  |
| Burr cells (echinocytes) | Uraemia<br>Pyruvate kinase deficiency |  |
| Acanthocytes | Abetalipoproteinemia |  |

Other blood film abnormalities:

- hypersegmented neutrophils: megaloblastic anaemia

# BLOOD FILMS: TYPICAL PICTURES

Hyposplenism e.g. post-splenectomy
- target cells
- Howell-Jolly bodies
- Pappenheimer bodies
- siderotic granules
- acanthocytes

Iron-deficiency anaemia
- target cells
- 'pencil' poikilocytes
- if combined with B12/folate deficiency a 'dimorphic' film occurs with mixed microcytic and macrocytic cells

Myelofibrosis
- 'tear-drop' poikilocytes

Intravascular haemolysis
- schistocytes

Megaloblastic anaemia
- hypersegmented neutrophils

# NORMOCYTIC ANAEMIA

Causes of normocytic anaemia include
- anaemia of chronic disease
- chronic kidney disease
- aplastic anaemia
- haemolytic anaemia
- acute blood loss

# MICROCYTIC ANAEMIA

Causes
1. iron-deficiency anaemia
2. thalassaemia*
3. congenital sideroblastic anaemia
4. anaemia of chronic disease (more commonly a normocytic, normochromic picture)
5. lead poisoning

A question sometimes seen in exams gives a history of a normal haemoglobin level associated with a microcytosis. In patients not at risk of thalassaemia, this should raise the possibility of polycythaemia rubra vera which may cause an iron-deficiency secondary to bleeding.

New onset microcytic anaemia in elderly patients should be urgently investigated to exclude underlying malignancy.

*in beta-thalassaemia minor the microcytosis is often disproportionate to the anaemia

# MACROCYTIC ANAEMIA

Macrocytic anaemia can be divided into causes associated with a megaloblastic bone marrow and those with a normoblastic bone marrow

| Megaloblastic causes | Normoblastic causes |
|---|---|
| • vitamin B12 deficiency<br>• folate deficiency | • alcohol<br>• liver disease<br>• hypothyroidism<br>• pregnancy<br>• reticulocytosis<br>• myelodysplasia<br>• drugs: cytotoxics |

# VITAMIN B12 DEFICIENCY

Vitamin B12 is mainly used in the body for red blood cell development and also maintenance of the nervous system. It is absorbed after binding to intrinsic factor (secreted from parietal cells in the stomach) and is actively absorbed in the terminal ileum. A small amount of vitamin B12 is passively absorbed without being bound to intrinsic factor.

Causes of vitamin B12 deficiency
- pernicious anaemia: most common cause
- post gastrectomy
- vegan diet or a poor diet
- disorders of terminal ileum (site of absorption): Crohn's, blind-loop etc
- metformin (rare)

Features of vitamin B12 deficiency
- macrocytic anaemia
- sore tongue and mouth
- neurological symptoms
  - the dorsal column is usually affected first (joint position, vibration) prior to distal paraesthesia
- neuropsychiatric symptoms: e.g. mood disturbances

Management
- if no neurological involvement 1 mg of IM hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months
- if a patient is also deficient in folic acid then it is important to treat the B12 deficiency first to avoid precipitating subacute combined degeneration of the cord

# SIDEROBLASTIC ANAEMIA

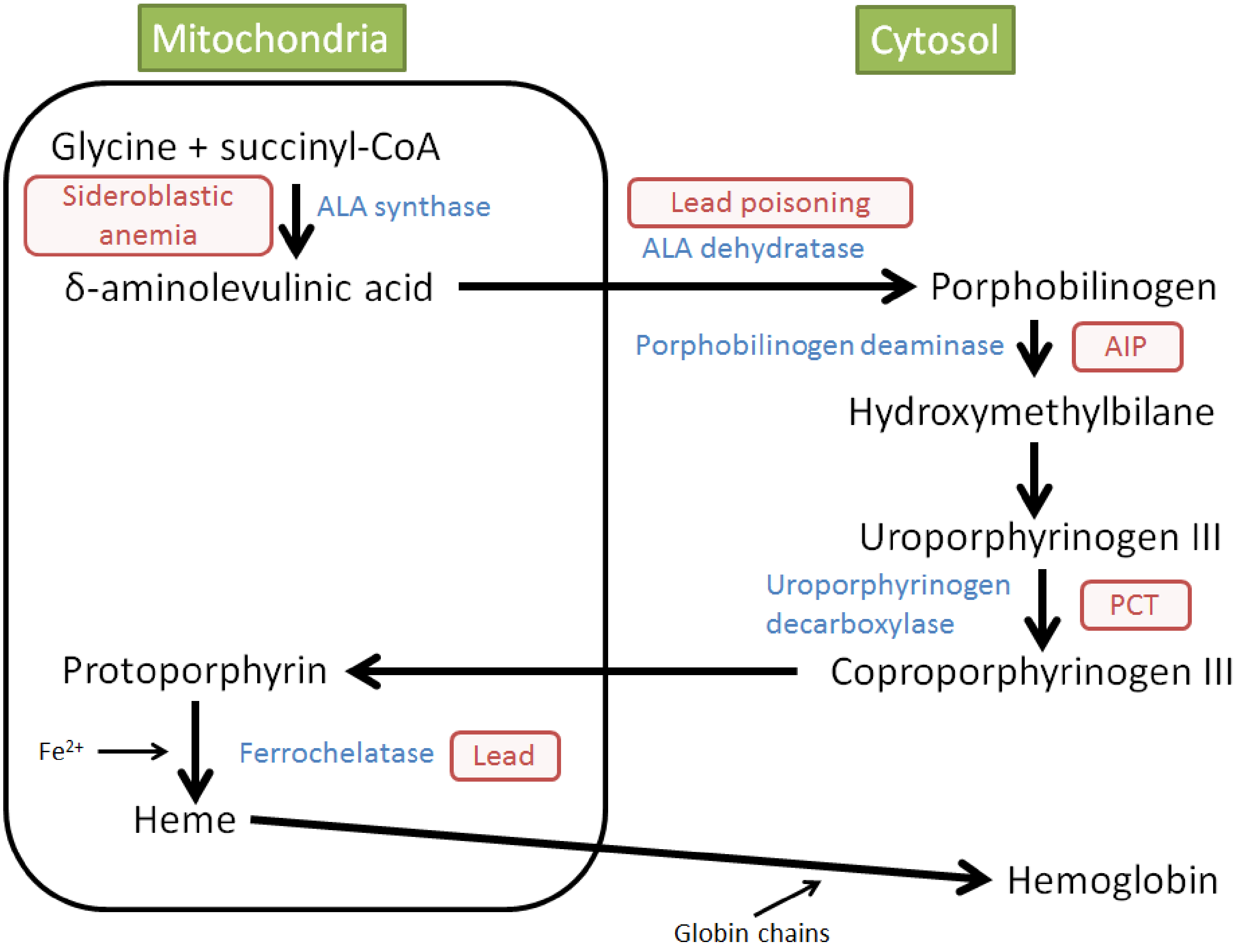
Sideroblastic anaemia is a condition where red cells fail to completely form haem, whose biosynthesis takes place partly in the mitochondrion. This leads to deposits of iron in the mitochondria that form a ring around the nucleus called a ring sideroblast. It may be congenital or acquired

Congenital cause: delta-aminolevulinate synthase-2 deficiency

Acquired causes
- myelodysplasia
- alcohol
- lead
- anti-TB medications

Investigations
- hypochromic microcytic anaemia (more so in congenital)
- bone marrow: sideroblasts and increased iron stores

Management
- supportive
- treat any underlying cause
- pyridoxine may help


Mitochondria
Cytosol
Glycine + succinyl-CoA
Sideroblastic anemia
ALA synthase
δ-aminolevulinic acid
Lead poisoning
ALA dehydratase
Porphobilinogen
Porphobilinogen deaminase
AIP
Hydroxymethylbilane
Uroporphyrinogen III
Uroporphyrinogen decarboxylase
PCT
Coproporphyrinogen III
Protoporphyrin
Fe²⁺
Ferrochelatase
Lead
Heme
Hemoglobin
Globin chains

## FANCONI ANAEMIA

Autosomal recessive.

Features
- haematological:

    - aplastic anaemia
    - increased risk of acute myeloid leukaemia
- neurological
- skeletal abnormalities:
    - short stature
    - thumb/radius abnormalities
- cafe au lait spots

# HAEMOLYTIC ANAEMIAS: BY SITE

In intravascular haemolysis free haemoglobin is released which binds to haptoglobin. As haptoglobin becomes saturated haemoglobin binds to albumin forming methaemalbumin (detected by Schumm's test). Free haemoglobin is excreted in the urine as haemoglobinuria, haemosiderinuria

Intravascular haemolysis: causes
- mismatched blood transfusion
- G6PD deficiency*
- red cell fragmentation: heart valves, TTP, DIC, HUS
- paroxysmal nocturnal haemoglobinuria
- cold autoimmune haemolytic anaemia

Extravascular haemolysis: causes
- haemoglobinopathies: sickle cell, thalassaemia
- hereditary spherocytosis
- haemolytic disease of newborn
- warm autoimmune haemolytic anaemia

*strictly speaking there is an element of extravascular haemolysis in G6PD as well, although it is usually classified as a intravascular cause

# AUTOIMMUNE HAEMOLYTIC ANAEMIA

Autoimmune haemolytic anaemia (AIHA) may be divided in to 'warm' and 'cold' types, according to at what temperature the antibodies best cause haemolysis. It is most commonly idiopathic but may be secondary to a lymphoproliferative disorder, infection or drugs. AIHA is characterised by a positive direct antiglobulin test (Coombs' test)

**Warm AIHA**
In warm AIHA the antibody (usually IgG) causes haemolysis best at body temperature and haemolysis tends to occur in extravascular sites, for example the spleen. Management options include steroids, immunosuppression and splenectomy

Causes of warm AIHA

- autoimmune disease: e.g. systemic lupus erythematosus*
- neoplasia: e.g. lymphoma, CLL
- drugs: e.g. methyldopa

**Cold AIHA**
The antibody in cold AIHA is usually IgM and causes haemolysis best at 4 deg C. Haemolysis is mediated by complement and is more commonly intravascular. Features may include symptoms of Raynaud's and acrocynaosis. Patients respond less well to steroids

Causes of cold AIHA

- neoplasia: e.g. lymphoma
- infections: e.g. mycoplasma, EBV

*systemic lupus erythematosus can rarely be associated with a mixed-type autoimmune haemolytic anaemia

## APLASTIC ANAEMIA: MANAGEMENT

Supportive

- blood products
- prevention and treatment of infection

Anti-thymocyte globulin (ATG) and anti-lymphocyte globulin (ALG)

- prepared in animals (e.g. rabbits or horses) by injecting human lymphocytes
- is highly allergenic and may cause serum sickness (fever, rash, arthralgia), therefore steroid cover usually given
- immunosuppression using agents such as ciclosporin may also be given

Stem cell transplantation

- allogeneic transplants have a success rate of up to 80%

# SICKLE-CELL ANAEMIA

Sickle-cell anaemia is an autosomal recessive condition that results for synthesis of an abnormal haemoglobin chain termed HbS. It is more common in people of African descent as the heterozygous condition offers some protection against malaria. Around 10% of UK Afro-Caribbean's are carriers of HbS (i.e. heterozygous). Such people are only symptomatic if severely hypoxic.

Symptoms in homozygotes don't tend to develop until 4-6 months when the abnormal HbSS molecules take over from fetal haemoglobin.

Pathophysiology

- polar amino acid glutamate is substituted by non-polar valine in each of the two beta chains (codon 6). This decreases the water solubility of deoxy-Hb
- in the deoxygenated state the HbS molecules polymerise and cause RBCs to sickle
- HbAS patients sickle at p02 2.5 - 4 kPa, HbSS patients at p02 5 - 6 kPa
- sickle cells are fragile and haemolyse; they block small blood vessels and cause infarction

Investigations

- definitive diagnosis of sickle cell disease is by haemoglobin electrophoresis

# SICKLE-CELL ANAEMIA: MANAGEMENT

Crisis management

- analgesia e.g. opiates
- rehydrate
- oxygen
- consider antibiotics if evidence of infection
- blood transfusion
- exchange transfusion: e.g. if neurological complications

Longer-term management

- hydroxyurea
- increases the HbF levels and is used in the prophylactic management of sickle cell anaemia to prevent painful episodes
- NICE CKS suggest that sickle cell patients should receive the pneumococcal polysaccharide vaccine every 5 years

# SICKLE-CELL CRISES

Sickle cell anaemia is characterised by periods of good health with intervening crises

A number of types of crises are recognised:
- thrombotic, 'painful crises'
- sequestration
- acute chest syndrome
- aplastic
- haemolytic

Thrombotic crises
- also known as painful crises or vaso-occlusive crises
- precipitated by infection, dehydration, deoxygenation
- infarcts occur in various organs including the bones (e.g. avascular necrosis of hip, hand-foot syndrome in children, lungs, spleen and brain

Sequestration crises
- sickling within organs such as the spleen or lungs causes pooling of blood with worsening of the anaemia

Acute chest syndrome
- dyspnoea, chest pain, pulmonary infiltrates, low pO2
- the most common cause of death after childhood

Aplastic crises
- caused by infection with parvovirus
- sudden fall in haemoglobin

Haemolytic crises
- rare
- fall in haemoglobin due an increased rate of haemolysis

# SPLENOMEGALY

Massive splenomegaly
- myelofibrosis
- chronic myeloid leukaemia
- visceral leishmaniasis (kala-azar)
- malaria
- Gaucher's syndrome

Other causes (as above plus)
- portal hypertension e.g. secondary to cirrhosis
- lymphoproliferative disease e.g. CLL, Hodgkin's
- haemolytic anaemia
- infection: hepatitis, glandular fever
- infective endocarditis
- sickle-cell*, thalassaemia
- rheumatoid arthritis (Felty's syndrome)

*the majority of adults patients with sickle-cell will have an atrophied spleen due to repeated infarction

## HYPOSPLENISM

Causes
- splenectomy
- sickle-cell
- coeliac disease, dermatitis herpetiformis
- Graves' disease
- systemic lupus erythematosus
- amyloid

Features
- Howell-Jolly bodies
- Siderocytes

# THROMBOCYTOSIS

Thrombocytosis is an abnormally high platelet count, usually > 400 * 109/l.

Causes of thrombocytosis
- reactive: platelets are an acute phase reactant - platelet count can increase in response to stress such as a severe infection, surgery. Iron deficiency anaemia can also cause a reactive thrombocytosis
- malignancy
- essential thrombocytosis (see below), or as part of another myeloproliferative disorder such as chronic myeloid leukaemia or polycythaemia rubra vera
- hyposplenism

**Essential thrombocytosis**
Essential thrombocytosis is one of the myeloproliferative disorders which overlaps with chronic myeloid leukaemia, polycythaemia rubra vera and myelofibrosis. Megakaryocyte proliferation results in an overproduction of platelets.

Features
- platelet count > 600 * 109/l
- both thrombosis (venous or arterial) and haemorrhage can be seen
- a characteristic symptom is a burning sensation in the hands
- a JAK2 mutation is found in around 50% of patients

Management
- hydroxyurea (hydroxycarbamide) is widely used to reduce the platelet count
- interferon-α is also used in younger patients
- low-dose aspirin may be used to reduce the thrombotic risk

# THROMBOTIC THROMBOCYTOPENIC PURPURA

Pathogenesis of thrombotic thrombocytopenic purpura (TTP)
- abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels
- in TTP there is a deficiency of ADAMTS13 (a metalloprotease enzyme) which breakdowns ('cleaves') large multimers of von Willebrand's factor
- overlaps with haemolytic uraemic syndrome (HUS)

Features
- rare, typically adult females
- fever

- fluctuating neuro signs (microemboli)
- microangiopathic haemolytic anaemia
- thrombocytopenia
- renal failure

Causes
- post-infection e.g. urinary, gastrointestinal
- pregnancy
- drugs: ciclosporin, oral contraceptive pill, penicillin, clopidogrel, aciclovir
- tumours
- SLE
- HIV

## THROMBOTIC THROMBOCYTOPENIC PURPURA: MANAGEMENT

Pathogenesis of thrombotic thrombocytopenic purpura (TTP)
- abnormally large and sticky multimers of von Willebrand's factor cause platelets to clump within vessels
- in TTP there is a deficiency of protease which breakdowns large multimers of von Willebrand's factor
- overlaps with haemolytic uraemic syndrome (HUS)

Management
- no antibiotics - may worsen outcome
- plasma exchange is the treatment of choice
- steroids, immunosuppressants
- vincristine

## IMMUNE THROMBOCYTOPENIA (ITP) IN ADULTS

Immune (or idiopathic) thrombocytopenic purpura (ITP) is an immune-mediated reduction in the platelet count. Antibodies are directed against the glycoprotein IIb/IIIa or Ib-V-IX complex.

ITP can be divided into acute and chronic forms:

Acute ITP
- more commonly seen in children
- equal sex incidence
- may follow an infection or vaccination
- usually runs a self-limiting course over 1-2 weeks

Chronic ITP
- more common in young/middle-aged women
- tends to run a relapsing-remitting course

Evan's syndrome
- ITP in association with autoimmune haemolytic anaemia (AIHA)

# ITP: INVESTIGATION AND MANAGEMENT

Idiopathic thrombocytopenic purpura (ITP) is an immune mediated reduction in the platelet count. Antibodies are directed against the glycoprotein IIb-IIIa or Ib complex

Investigations
- antiplatelet autoantibodies (usually IgG)
- bone marrow aspiration shows megakaryocytes in the marrow. This should be carried out prior to the commencement of steroids in order to rule out leukaemia

Management
- oral prednisolone (80% of patients respond)
- splenectomy if platelets < 30 after 3 months of steroid therapy
- IV immunoglobulins
- immunosuppressive drugs e.g. cyclophosphamide

# CYCLOPHOSPHAMIDE

Cyclophosphamide is an alkylating agent used in the management of cancer and autoimmune conditions. It works by causing cross-linking of DNA

Adverse effects
- haemorrhagic cystitis: incidence reduced by the use of hydration and mesna
- myelosuppression
- transitional cell carcinoma

Mesna
- 2-mercaptoethane sulfonate Na
- a metabolite of cyclophosphamide called acrolein is toxic to urothelium
- mesna binds to and inactivates acrolein helping to prevent haemorrhagic cystitis

# NEUTROPAENIA

Causes
- viral
- drugs e.g. carbimazole, clozapine
- haematological malignancy
- aplastic anemia
- haemodialysis

Benign ethnic neutropaenia is common in people of black African and Afro-Caribbean ethnicity and requires no treatment.

# NEUTROPENIC SEPSIS

Neutropenic sepsis is a relatively common complication of cancer therapy, usually as a consequence of chemotherapy. It most commonly occurs 7-14 days after chemotherapy. It may be defined as a neutrophil count of < 0.5 * 109 in a patient who is having anticancer treatment and has one of the following:
- a temperature higher than 38ºC or
- other signs or symptoms consistent with clinically significant sepsis

Prophylaxis
- if it is anticipated that patients are likely to have a neutrophil count of < 0.5 * 109 as a consequence of their treatment they should be offered a fluoroquinolone

Management
- antibiotics must be started immediately, do not wait for the WBC
- NICE recommends starting empirical antibiotic therapy with piperacillin with tazobactam (Tazocin) immediately
- many units add vancomycin if the patient has central venous access but NICE do not support this approach
- following this initial treatment patients are usually assessed by a specialist and risk-stratified to see if they may be able to have outpatient treatment
- if patients are still febrile and unwell after 48 hours an alternative antibiotic such as meropenem is often prescribed +/- vancomycin
- if patients are not responding after 4-6 days the Christie guidelines suggest ordering investigations for fungal infections (e.g. HRCT), rather than just starting therapy antifungal therapy blindly
- there may be a role for G-CSF in selected patients

# POLYCYTHAEMIA

Polycythaemia may be relative, primary (polycythaemia rubra vera) or secondary

Relative causes
- dehydration
- stress: Gaisbock syndrome

Primary
- polycythaemia rubra vera

Secondary causes
- COPD
- altitude
- obstructive sleep apnoea
- excessive erythropoietin: cerebellar haemangioma, hypernephroma, hepatoma, uterine fibroids*

To differentiate between true (primary or secondary) polycythaemia and relative polycythaemia red cell mass studies are sometimes used. In true polycythaemia the total red cell mass in males > 35 ml/kg and in women > 32 ml/kg

*uterine fibroids may cause menorrhagia which in turn leads to blood loss - polycythaemia is rarely a clinical problem

# POLYCYTHAEMIA VERA: FEATURES

Polycythaemia vera (previously called polycythaemia rubra vera) is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an increase in red cell volume, often accompanied by overproduction of neutrophils and platelets. It has recently been established that a mutation in JAK2 is present in approximately 95% of patients with polycythaemia vera and this has resulted in significant changes to the diagnostic criteria. The incidence of polycythaemia vera peaks in the sixth decade.

Features
- hyperviscosity
- pruritus, typically after a hot bath
- splenomegaly
- haemorrhage (secondary to abnormal platelet function)
- plethoric appearance
- hypertension in a third of patients
- low ESR

Following history and examination, the British Committee for Standards in Haematology (BCSH) recommend the following tests are performed

- full blood count/film (raised haematocrit; neutrophils, basophils, platelets raised in half of patients)
- JAK2 mutation
- serum ferritin
- renal and liver function tests

If the JAK2 mutation is negative and there is no obvious secondary causes the BCSH suggest the following tests:

- red cell mass
- arterial oxygen saturation
- abdominal ultrasound
- serum erythropoietin level
- bone marrow aspirate and trephine
- cytogenetic analysis
- erythroid burst-forming unit (BFU-E) culture

Other features that may be seen in PRV include a low ESR and a raised leukocyte alkaline phosphatase

The diagnostic criteria for polycythaemia vera have recently been updated by the BCSH. This replaces the previous polycythaemia vera Study Group criteria.

JAK2-positive polycythaemia vera - diagnosis requires both criteria to be present

| Criteria | Notes |
|---|---|
| A1 | High haematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted) |
| A2 | Mutation in JAK2 |

JAK2-negative PRV - diagnosis requires A1 + A2 + A3 + either another A or two B criteria

| Criteria | Notes |
|---|---|
| A1 | Raised red cell mass (>25% above predicted) OR haematocrit >0.60 in men, >0.56 in women |
| A2 | Absence of mutation in JAK2 |
| A3 | No cause of secondary erythrocytosis |
| A4 | Palpable splenomegaly |
| A5 | Presence of an acquired genetic abnormality (excluding BCR-ABL) in the haematopoietic cells |
| B1 | Thrombocytosis (platelet count >450 * $10^9$/l) |
| B2 | Neutrophil leucocytosis (neutrophil count > 10 * $10^9$/l in non-smokers; > 12.5*$10^9$/l in smokers) |
| B3 | Radiological evidence of splenomegaly |

| Criteria | Notes |
|---|---|
| B4 | Endogenous erythroid colonies or low serum erythropoietin |

# POLYCYTHAEMIA VERA: MANAGEMENT

Polycythaemia vera is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an increase in red cell volume, often accompanied by overproduction of neutrophils and platelets. It has peak incidence in the sixth decade, with typical features including hyperviscosity, pruritus and splenomegaly

Management
- aspirin
- venesection - first line treatment
- hydroxyurea -slight increased risk of secondary leukaemia
- phosphorus-32 therapy

Prognosis
- thrombotic events are a significant cause of morbidity and mortality
- 5-15% of patients progress to myelofibrosis
- 5-15% of patients progress to acute leukaemia (risk increased with chemotherapy treatment)

# BETA-THALASSAEMIA TRAIT

The thalassaemias are a group of genetic disorders characterised by a reduced production rate of either alpha or beta chains. Beta-thalassaemia trait is an autosomal recessive condition characterised by a mild hypochromic, microcytic anaemia. It is usually asymptomatic

Features
- mild hypochromic, microcytic anaemia - microcytosis is characteristically disproportionate to the anaemia
- HbA2 raised (> 3.5%)

# BETA-THALASSAEMIA MAJOR

Overview
- absence of beta chains
- chromosome 11

Features
- presents in first year of life with failure to thrive and hepatosplenomegaly
- microcytic anaemia
- HbA2 & HbF raised
- HbA absent

Management
- repeated transfusion → iron overload
- s/c infusion of desferrioxamine

# G6PD DEFICIENCY

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the commonest red blood cell enzyme defect. It is more common in people from the Mediterranean and Africa and is inherited in an X-linked recessive fashion. Many drugs can precipitate a crisis as well as infections and broad (fava) beans

Pathophysiology

- G6PD is the first step in the pentose phosphate pathway, which converts glucose-6-phosphate→ 6-phosphogluconolactone
  - this reaction also results in nicotinamide adenine dinucleotide phosphate (NADP) → NADPH
  - i.e. glucose-6-phosphate + NADP → 6-phosphogluconolactone + NADPH
- NADPH is important for converting oxidizied glutathine back to it's reduced form
- reduced glutathine protects red blood cells from oxidative damage by oxidants such as superoxide anion (O2-) and hydrogen peroxide
- ↓ G6PD → ↓ reduced NADPH → ↓ reduced glutathione → increased red cell susceptibility to oxidative stress

Features

- neonatal jaundice is often seen
- intravascular haemolysis
- gallstones are common
- splenomegaly may be present
- Heinz bodies on blood films. Bite and blister cells may also be seen

Diagnosis is made by using a G6PD enzyme assay

Some drugs causing haemolysis

- anti-malarials: primaquine
- ciprofloxacin
- sulph- group drugs: sulphonamides, sulphasalazine, sulfonylureas

Some drugs thought to be safe

- penicillins
- cephalosporins
- macrolides
- tetracyclines
- trimethoprim

# HEREDITARY SPHEROCYTOSIS

Basics

- most common hereditary haemolytic anaemia in people of northern European descent
- autosomal dominant defect of red blood cell cytoskeleton
- the normal biconcave disc shape is replaced by a sphere-shaped red blood cell
- red blood cell survival reduced as destroyed by the spleen

Presentation

- failure to thrive
- jaundice, gallstones
- splenomegaly
- aplastic crisis precipitated by parvovirus infection
- degree of haemolysis variable
- MCHC elevated

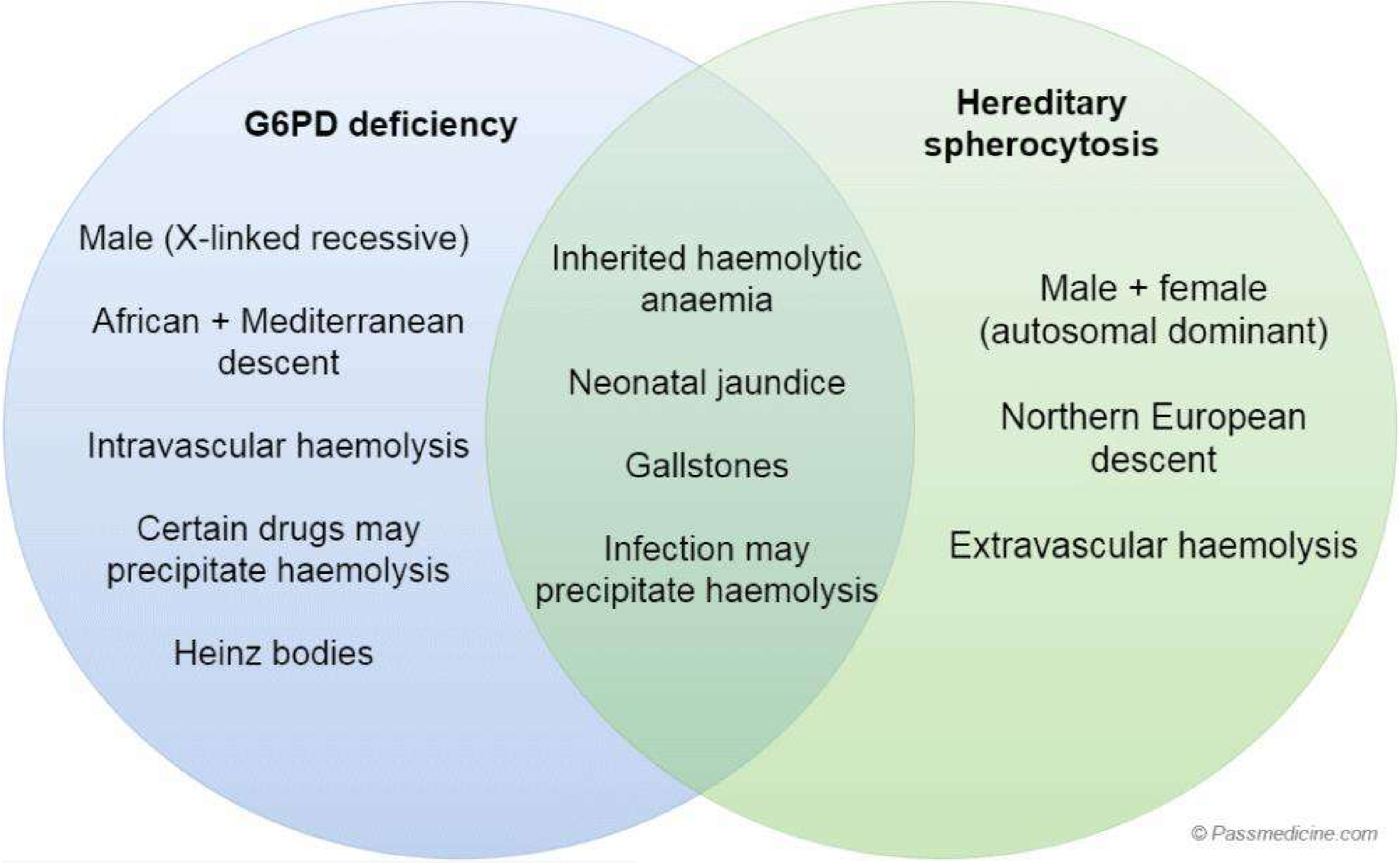
Diagnosis

- the osmotic fragility test was previously the recommend investigation of choice. However, it is now deemed unreliable and is no longer recommended
- the British Journal of Haematology (BJH) guidelines state that *'patients with a family history of HS, typical clinical features and laboratory investigations (spherocytes, raised mean corpuscular haemoglobin concentration[MCHC], increase in reticulocytes) do not require any additional tests*
- if the diagnosis is equivocal the BJH recommend the cryohaemolysis test and EMA binding
- for atypical presentations electrophoresis analysis of erythrocyte membranes is the method of choice

Management

- acute haemolytic crisis:
  - treatment is generally supportive
  - transfusion if necessary
- longer term treatment:
  - folate replacement
  - splenectomy

# COMPARING G6PD DEFICIENCY TO HEREDITARY SPHEROCYTOSIS:


G6PD deficiency
Hereditary spherocytosis
Male (X-linked recessive)
African + Mediterranean descent
Intravascular haemolysis
Certain drugs may precipitate haemolysis
Heinz bodies
Inherited haemolytic anaemia
Neonatal jaundice
Gallstones
Infection may precipitate haemolysis
Male + female (autosomal dominant)
Northern European descent
Extravascular haemolysis
© Passmedicine.com

Comparison of G6PD deficiency to hereditary spherocytosis

| | G6PD deficiency | Hereditary spherocytosis |
|---|---|---|
| **Gender** | Male (X-linked recessive) | Male + female (autosomal dominant) |
| **Ethnicity** | African + Mediterranean descent | Northern European descent |
| **Typical history** | • Neonatal jaundice<br>• Infection/drugs precipitate haemolysis<br>• Gallstones | • Neonatal jaundice<br>• Chronic symptoms although haemolytic crises may be precipitated by infection<br>• Gallstones<br>• Splenomegaly is common |
| **Blood film** | Heinz bodies | Spherocytes (round, lack of central pallor) |
| **Diagnostic test** | Measure enzyme activity of G6PD | Osmotic fragility test |

# PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired disorder leading to haemolysis (mainly intravascular) of haematological cells. It is thought to be caused by increased sensitivity of cell membranes to complement (see below) due to a lack of glycoprotein glycosyl-phosphatidylinositol (GPI). Patients are more prone to venous thrombosis

Pathophysiology
- GPI can be thought of as an anchor which attaches surface proteins to the cell membrane
- complement-regulating surface proteins, e.g. decay-accelerating factor (DAF), are not properly bound to the cell membrane due a lack of GPI
- thrombosis is thought to be caused by a lack of CD59 on platelet membranes predisposing to platelet aggregation

Features
- haemolytic anaemia
- red blood cells, white blood cells, platelets or stem cells may be affected therefore pancytopaenia may be present
- haemoglobinuria: classically dark-coloured urine in the morning (although has been shown to occur throughout the day)
- thrombosis e.g. Budd-Chiari syndrome
- aplastic anaemia may develop in some patients

Diagnosis
- flow cytometry of blood to detect low levels of CD59 and CD55 has now replaced Ham's test as the gold standard investigation in PNH
- Ham's test: acid-induced haemolysis (normal red cells would not)

Management
- blood product replacement
- anticoagulation
- eculizumab, a monoclonal antibody directed against terminal protein C5, is currently being trialled and is showing promise in reducing intravascular haemolysis
- stem cell transplantation

# METHAEMOGLOBINAEMIA

Methaemoglobinaemia describes haemoglobin which has been oxidised from Fe2+ to Fe3+. This is normally regulated by NADH methaemoglobin reductase, which transfers electrons from NADH to methaemoglobin resulting in the reduction of methaemoglobin to haemoglobin. There is tissue hypoxia as Fe3+ cannot bind oxygen, and hence the oxidation dissociation curve is moved to the left

Congenital causes

- haemoglobin chain variants: HbM, HbH
- NADH methaemoglobin reductase deficiency

Acquired causes

- drugs: sulphonamides, nitrates (including recreational nitrates e.g. amyl nitrite 'poppers'), dapsone, sodium nitroprusside, primaquine
- chemicals: aniline dyes

Features

- 'chocolate' cyanosis
- dyspnoea, anxiety, headache
- severe: acidosis, arrhythmias, seizures, coma
- normal pO2 but decreased oxygen saturation

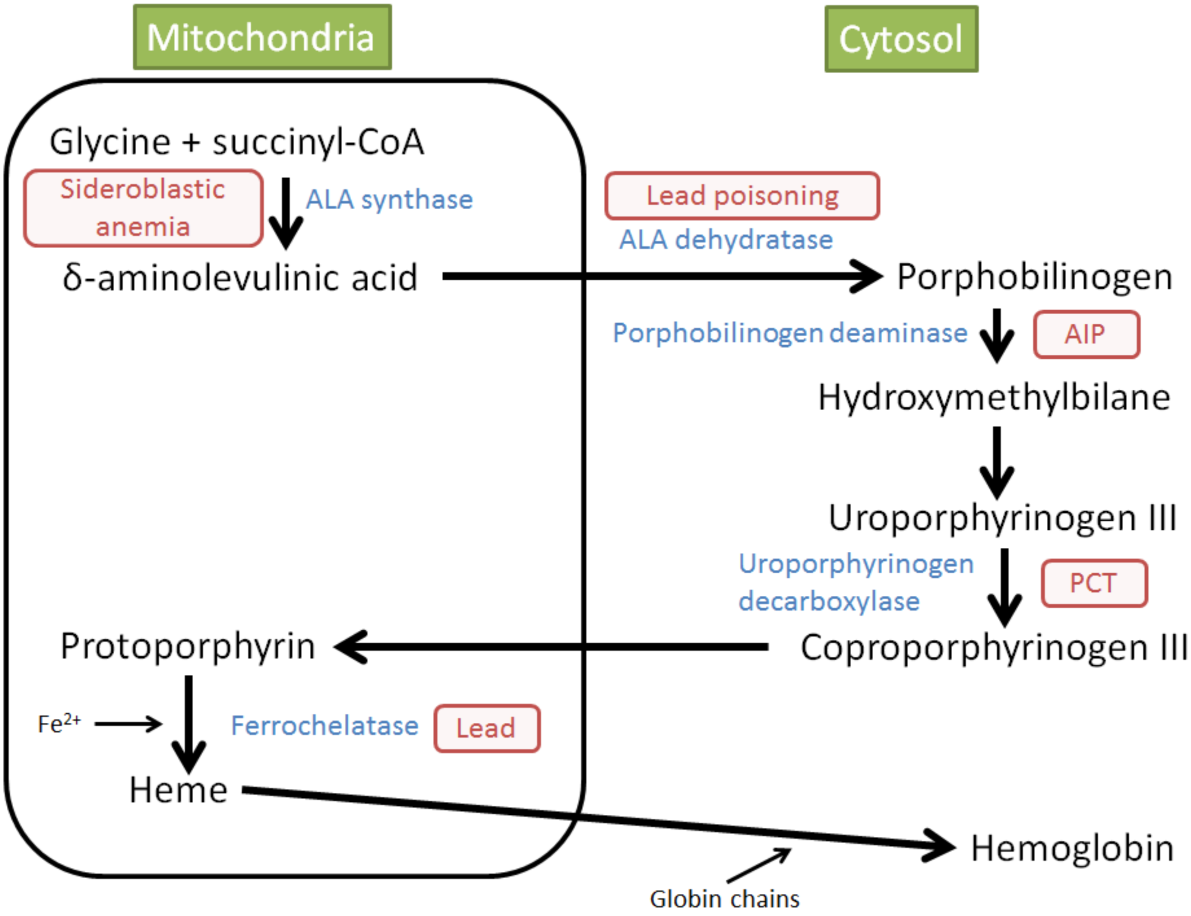
Management

- NADH - methaemoglobinaemia reductase deficiency: ascorbic acid
- IV methylthioninium chloride (methylene blue) if acquired

# PORPHYRIAS

Overview

- abnormality in enzymes responsible for the biosynthesis of haem
- results in overproduction of intermediate compounds (porphyrins)
- may be acute or non-acute


Mitochondria
Cytosol
Glycine + succinyl-CoA
Sideroblastic anemia
ALA synthase
δ-aminolevulinic acid
Lead poisoning
ALA dehydratase
Porphobilinogen
Porphobilinogen deaminase
AIP
Hydroxymethylbilane
Uroporphyrinogen III
Uroporphyrinogen decarboxylase
PCT
Coproporphyrinogen III
Protoporphyrin
Fe2+
Ferrochelatase
Lead
Heme
Hemoglobin
Globin chains

Acute intermittent porphyria (AIP)

- autosomal dominant
- defect in porphobilinogen deaminase
- female and 20-40 year olds more likely to be affected
- typically present with abdominal symptoms, neuropsychiatric symptoms
- hypertension and tachycardia common
- urine turns deep red on standing

Porphyria cutanea tarda (PCT)

- most common hepatic porphyria
- defect in uroporphyrinogen decarboxylase
- may be caused by hepatocyte damage e.g. alcohol, oestrogens
- classically photosensitive rash with bullae, skin fragility on face and dorsal aspect of hands

- urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp
- manage with chloroquine

Variegate porphyria

- autosomal dominant
- defect in protoporphyrinogen oxidase
- photosensitive blistering rash
- abdominal and neurological symptoms
- more common in South Africans

# ACUTE INTERMITTENT PORPHYRIA

Acute intermittent porphyria (AIP) is a rare autosomal dominant condition caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem. The results in the toxic accumulation of delta aminolaevulinic acid and porphobilinogen. It characteristically presents with abdominal and neuropsychiatric symptoms in 20-40 year olds. AIP is more common in females (5:1)

The classical presentation is a combination of abdominal, neurological and psychiatric symptoms:

- abdominal: abdominal pain, vomiting
- neurological: motor neuropathy
- psychiatric: e.g. depression
- hypertension and tachycardia common

Diagnosis

- classically urine turns deep red on standing
- raised urinary porphobilinogen (elevated between attacks and to a greater extent during acute attacks)
- assay of red cells for porphobilinogen deaminase
- raised serum levels of delta aminolaevulinic acid and porphobilinogen

# HAEMOPHILIA

Haemophilia is a X-linked recessive disorder of coagulation. Up to 30% of patients have no family history of the condition. Haemophilia A is due to a deficiency of factor VIII whilst in haemophilia B (Christmas disease) there is a lack of factor IX

Features
- haemoarthroses, haematomas
- prolonged bleeding after surgery or trauma

Blood tests
- prolonged APTT
- bleeding time, thrombin time, prothrombin time normal

Up to 10-15% of patients with haemophilia A develop antibodies to factor VIII treatment.

# VON WILLEBRAND'S DISEASE

Von Willebrand's disease is the most common inherited bleeding disorder. The majority of cases are inherited in an autosomal dominant fashion* and characteristically behaves like a platelet disorder i.e. epistaxis and menorrhagia are common whilst haemoarthroses and muscle haematomas are rare

Role of von Willebrand factor
- large glycoprotein which forms massive multimers up to 1,000,000 Da in size
- promotes platelet adhesion to damaged endothelium
- carrier molecule for factor VIII

Types
type 1: partial reduction in vWF (80% of patients)
type 2*: abnormal form of vWF
type 3**: total lack of vWF (autosomal recessive)

Investigation
- prolonged bleeding time
- APTT may be prolonged
- factor VIII levels may be moderately reduced
- defective platelet aggregation with ristocetin

Management
- tranexamic acid for mild bleeding
- desmopressin (DDAVP): raises levels of vWF by inducing release of vWF from Weibel-Palade bodies in endothelial cells

- factor VIII concentrate

*type 2A VWD is caused by defective platelet adhesion due to decreased high molecular weight VWF multimers (i.e. the VWF protein is too small). Type 2B is characterised by a pathological increase of VWF-platelet interaction. Type 2M is caused by a decrease in VWF-platelet interaction (not related to loss of high molecular weight multimers). Type 2N is caused by abnormal binding of the VWF to Factor VIII. There is no clear correlation between symptomatic presentation and type of VWD however common themes amongst patients include excessive mucocutaneous bleeding, bruising in the absence of trauma and menorrhagia in females.

**type 3 von Willebrand's disease (most severe form) is inherited as an autosomal recessive trait. Around 80% of patients have type 1 disease

# CRYOGLOBULINAEMIA

Immunoglobulins which undergo reversible precipitation at 4 deg C, dissolve when warmed to 37 deg C. One-third of cases are idiopathic

Three types
- type I (25%): monoclonal
- type II (25%): mixed monoclonal and polyclonal: usually with rheumatoid factor (RF)
- type III (50%): polyclonal: usually with RF

Type I
- monoclonal - IgG or IgM
- associations: multiple myeloma, Waldenstrom macroglobulinaemia

Type II
- mixed monoclonal and polyclonal: usually with RF
- associations: hepatitis C, RA, Sjogren's, lymphoma

Type III
- polyclonal: usually with RF
- associations: rheumatoid arthritis, Sjogren's

Symptoms (if present in high concentrations)
- Raynaud's only seen in type I
- cutaneous: vascular purpura, distal ulceration, ulceration
- arthralgia
- renal involvement (diffuse glomerulonephritis)

Tests
- low complement (esp. C4)
- high ESR

Treatment
- immunosuppression
- plasmapheresis

# EOSINOPHILIA

Causes of eosinophilia may be divided into pulmonary, infective and other

Pulmonary causes
- asthma
- allergic bronchopulmonary aspergillosis
- Churg-Strauss syndrome
- Loffler's syndrome
- tropical pulmonary eosinophilia
- eosinophilic pneumonia
- hypereosinophilic syndrome

Infective causes
- schistosomiasis
- nematodes: Toxocara, Ascaris, Strongyloides
- cestodes: Echinococcus

Other causes
- drugs: sulfasalazine, nitrofurantoin
- psoriasis/eczema
- eosinophilic leukaemia (very rare)

# MGUS

Monoclonal gammopathy of undetermined significance (MGUS, also known as benign paraproteinaemia and monoclonal gammopathy) is a common condition that causes a paraproteinaemia and is often mistaken for myeloma. Differentiating features are listed below. Around 10% of patients eventually develop myeloma at 10 years, with 50% at 15 years

Features
- usually asymptomatic
- no bone pain or increased risk of infections
- around 10-30% of patients have a demyelinating neuropathy

Differentiating features from myeloma
- normal immune function
- normal beta-2 microglobulin levels
- lower level of paraproteinaemia than myeloma (e.g. < 30g/l IgG, or < 20g/l IgA)
- stable level of paraproteinaemia
- no clinical features of myeloma (e.g. lytic lesions on x-rays or renal disease)

# IGG4-RELATED DISEASE

IgG4-related disease has been described in virtually every organ system: the biliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium, and skin. The histopathological features are similar across organs, regardless of the site. IgG4-related disease is analogous to sarcoidosis, in which diverse organ manifestations are linked by similar histopathological characteristics. Raised concentrations of IgG4 in tissue and serum can be helpful in diagnosing IgG4 disease, but neither is a specific diagnostic marker.

Examples include:
- Riedel's Thyroiditis
- Autoimmune pancreatitis
- Mediastinal and Retroperitoneal Fibrosis
- Periaortitis/periarteritis/Inflammatory aortic aneurysm
- Kuttner's Tumour (submandibular glands) & Mikulicz Syndrome (salivary and lacrimal glands)
- Possibly sjogren's and primary biliary cirrhosis

# DRUG-INDUCED PANCYTOPAENIA

Drug causes of pancytopaenia
- cytotoxics
- antibiotics: trimethoprim, chloramphenicol
- anti-rheumatoid: gold, penicillamine
- carbimazole*
- anti-epileptics: carbamazepine
- sulphonylureas: tolbutamide

*causes both agranulocytosis and pancytopaenia

# DISSEMINATED INTRAVASCULAR COAGULATION - DIAGNOSIS

Under homeostatic conditions, coagulation and fibrinolysis are coupled. The activation of the coagulation cascade yields thrombin that converts fibrinogen to fibrin; the stable fibrin clot being the final product of hemostasis. The fibrinolytic system breaks down fibrinogen and fibrin. Activation of the fibrinolytic system generates plasmin (in the presence of thrombin), which is responsible for the lysis of fibrin clots. The breakdown of fibrinogen and fibrin results in polypeptides (fibrin degradation products). In a state of homeostasis, the presence of plasmin is critical, as it is the central proteolytic enzyme of coagulation and is also necessary for fibrinolysis.

In DIC, the processes of coagulation and fibrinolysis are dysregulated, and the result is widespread clotting with resultant bleeding. Regardless of the triggering event of DIC, once initiated, the pathophysiology of DIC is similar in all conditions. One critical mediator of DIC is the release of a transmembrane glycoprotein (tissue factor =TF). TF is present on the surface of many cell types (including endothelial cells, macrophages, and monocytes) and is not normally in contact with the general circulation, but is exposed to the circulation after vascular damage. For example, TF is released in response to exposure to cytokines (particularly interleukin 1), tumour necrosis factor, and endotoxin. This plays a major role in the development of DIC in septic conditions. TF is also abundant in tissues of the lungs, brain, and placenta. This helps to explain why DIC readily develops in patients with extensive trauma. Upon activation, TF binds with coagulation factors that then triggers the extrinsic pathway (via Factor VII) which subsequently triggers the intrinsic pathway (XII to XI to IX) of coagulation.

Causes of DIC
- sepsis
- trauma
- obstetric complications e.g. aminiotic fluid embolism or hemolysis, elevated liver function tests, and low platelets (HELLP syndrome)
- malignancy

**Diagnosis**
A typical blood picture includes:
- low platelets
- prolonged APTT, prothrombin and bleeding time
- fibrin degradation products are often raised
- schistocytes due to microangiopathic haemolytic anaemia

| Disorder | Prothrombin time | APTT | Bleeding time | Platelet count |
|---|---|---|---|---|
| Warfarin administration | Prolonged | Normal | Normal | Normal |
| Aspirin administration | Normal | Normal | Prolonged | Normal |
| Heparin | Often normal (may be prolonged) | Prolonged | Normal | Normal |
| DIC | Prolonged | Prolonged | Prolonged | Low |

# ANTIPHOSPHOLIPID SYNDROME: PREGNANCY

Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia. It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE)

In pregnancy the following complications may occur:

- recurrent miscarriage
- IUGR
- pre-eclampsia
- placental abruption
- pre-term delivery
- venous thromboembolism

Management

- low-dose aspirin should be commenced once the pregnancy is confirmed on urine testing
- low molecular weight heparin once a fetal heart is seen on ultrasound. This is usually discontinued at 34 weeks gestation
- these interventions increase the live birth rate seven-fold

# VENOUS THROMBOEMBOLISM: RISK FACTORS

Common predisposing factors include malignancy, pregnancy and the period following an operation. The comprehensive list below is partly based on the 2010 SIGN venous thromboembolism (VTE) guidelines:

General
- increased risk with advancing age
- obesity
- family history of VTE
- pregnancy (especially puerperium)
- immobility
- hospitalisation
- anaesthesia
- central venous catheter: femoral >> subclavian

Underlying conditions
- malignancy
- thrombophilia: e.g. Activated protein C resistance, protein C and S deficiency
- heart failure
- antiphospholipid syndrome
- Behcet's
- polycythaemia
- nephrotic syndrome
- sickle cell disease
- paroxysmal nocturnal haemoglobinuria
- hyperviscosity syndrome
- homocystinuria

Medication
- combined oral contraceptive pill: 3rd generation more than 2nd generation
- hormone replacement therapy: the risk of VTE is higher in women taking oestrogen + progestogen preparations compared to those taking oestrogen only preparations
- raloxifene and tamoxifen
- antipsychotics (especially olanzapine) have recently been shown to be a risk factor

It should be remembered however that around 40% of patients diagnosed with a PE have no major risk factors.

# DEEP VEIN THROMBOSIS: DIAGNOSIS AND MANAGEMENT

NICE updated their guidelines on the investigation and management of venous thromboembolism (VTE) in 2020. Some of the key changes include recommending the following:

- the use of direct oral anticoagulants (DOACs) as first-line treatment for most people with VTE
- the use of DOACs in patients with active cancer, as opposed to low-molecular weight heparin as was the previous recommendation
- routine cancer screening is no longer recommended following a VTE diagnosis

If a patient is suspected of having a DVT a two-level DVT Wells score should be performed:

**Two-level DVT Wells score**

| Clinical feature | Points |
|---|---|
| Active cancer (treatment ongoing, within 6 months, or palliative) | 1 |
| Paralysis, paresis or recent plaster immobilisation of the lower extremities | 1 |
| Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia | 1 |
| Localised tenderness along the distribution of the deep venous system | 1 |
| Entire leg swollen | 1 |
| Calf swelling at least 3 cm larger than asymptomatic side | 1 |
| Pitting oedema confined to the symptomatic leg | 1 |
| Collateral superficial veins (non-varicose) | 1 |
| Previously documented DVT | 1 |
| An alternative diagnosis is at least as likely as DVT | -2 |

Clinical probability simplified score

- DVT likely: 2 points or more
- DVT unlikely: 1 point or less

If a DVT is 'likely' (2 points or more)

- a proximal leg vein ultrasound scan should be carried out within 4 hours
    - if the result is positive then a diagnosis of DVT is made and anticoagulant treatment should start
    - if the result is negative a D-dimer test should be arranged. A negative scan and negative D-dimer makes the diagnosis unlikely and alternative diagnoses should be considered
- if a proximal leg vein ultrasound scan cannot be carried out within 4 hours a D-dimer test should be performed and interim therapeutic anticoagulation administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)
    - interim therapeutic anticoagulation used to mean giving low-molecular weight heparin
    - NICE updated their guidance in 2020. They now recommend using an anticoagulant that can be continued if the result is positive.
    - this means normally a direct oral anticoagulant (DOAC) such as apixaban or rivaroxaban

- if the scan is negative but the D-dimer is positive:
    - stop interim therapeutic anticoagulation
    - offer a repeat proximal leg vein ultrasound scan 6 to 8 days later

If a DVT is 'unlikely' (1 point or less)

- perform a D-dimer test
    - this should be done within 4 hours. If not, interim therapeutic anticoagulation should be given until the result is available
    - if the result is negative then DVT is unlikely and alternative diagnoses should be considered
    - if the result is positive then a proximal leg vein ultrasound scan should be carried out within 4 hours
    - if a proximal leg vein ultrasound scan cannot be carried out within 4 hours interim therapeutic anticoagulation should be administered whilst waiting for the proximal leg vein ultrasound scan (which should be performed within 24 hours)

D-dimer tests

- NICE recommend either a point-of-care (finger prick) or laboratory-based test
- age-adjusted cut-offs should be used for patients > 50 years old

**Management**

The cornerstone of VTE management is anticoagulant therapy. This was historically done with warfarin, often preceded by heparin until the INR was stable. However, the development of DOACs, and an evidence base supporting their efficacy, has changed modern management.

Choice of anticoagulant

- the big change in the 2020 guidelines was the increased use of DOACs
- apixaban or rivaroxaban (both DOACs) should be offered first-line following the diagnosis of a DVT
    - instead of using low-molecular weight heparin (LMWH) until the diagnosis is confirmed, NICE now advocate using a DOAC once a diagnosis is suspected, with this continued if the diagnosis is confirmed
    - if neither apixaban or rivaroxaban are suitable then either LMWH followed by dabigatran or edoxaban OR LMWH followed by a vitamin K antagonist (VKA, i.e. warfarin)
- if the patient has active cancer
    - previously LMWH was recommended
    - the new guidelines now recommend using a DOAC, unless this is contraindicated
- if renal impairment is severe (e.g. < 15/min) then LMWH, unfractionated heparin or LMWH followed by a VKA
- if the patient has antiphospholipid syndrome (specifically 'triple positive' in the guidance) then LMWH followed by a VKA should be used

Length of anticoagulation

- all patients should have anticoagulation for at least 3 months

- continuing anticoagulation after this period is partly determined by whether the VTE was provoked or unprovoked
    - a provoked VTE is due to an obvious precipitating event e.g. immobilisation following major surgery. The implication is that this event was transient and the patient is no longer at increased risk
    - an unprovoked VTE occurs in the absence of an obvious precipitating event, i.e. there is a possibility that there are unknown factors (e.g. mild thrombophilia) making the patient more at risk from further clots
- if the VTE was provoked the treatment is typically stopped after the initial 3 months (3 to 6 months for people with active cancer)
- if the VTE was unprovoked then treatment is typically continued for up to 3 further months (i.e. 6 months in total)
    - NICE recommend that whether a patient has a total of 3-6 months anticoagulant is based upon balancing a person's risk of VTE recurrence and their risk of bleeding
    - the HAS-BLED score can be used to help assess the risk of bleeding
    - NICE state: 'Explain to people with unprovoked DVT or PE and a low bleeding risk that the benefits of continuing anticoagulation treatment are likely to outweigh the risks. '. The implication of this is that in the absence of a bleeding risk factors, patients are generally better off continuing anticoagulation for a total of 6 months

Thrombophilia screening

- not offered if patients will be on lifelong warfarin (i.e. won't alter management)
- consider testing for antiphospholipid antibodies if unprovoked DVT or PE
- consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE

# PREGNANCY: DVT/PE

Overview

- pregnancy is a hypercoagulable state
- majority occur in last trimester

Pathophysiology

- increase in factors VII, VIII, X and fibrinogen
- decrease in protein S
- uterus presses on IVC causing venous stasis in legs

Management

- warfarin contraindicated
- S/C low-molecular weight heparin preferred to IV heparin (less bleeding and thrombocytopenia)

## THROMBOPHILIA: CAUSES

Inherited

Gain of function polymorphisms
factor V Leiden (activated protein C resistance): most common cause of thrombophilia
prothrombin gene mutation: second most common cause

Deficiencies of naturally occurring anticoagulants
antithrombin III deficiency
protein C deficiency
protein S deficiency

The table below shows the prevalence and relative risk of venous thromboembolism (VTE) of the different inherited thrombophilias:

## FACTOR V LEIDEN

Factor V Leiden (activated protein C resistance) is the most common inherited thrombophilia, being present in around 5% of the UK population.

It is due to a gain of function mutation in the Factor V Leiden protein. The result of the mis-sense mutation is that activated factor V (a clotting factor) is inactivated 10 times more slowly by activated protein C than normal. This explains the alternative name for factor V Leiden of activated protein C resistance,

Heterozygotes have a 4-5 fold risk of venous thrombosis. Homozygotes have a 10 fold risk of venous thrombosis but the prevalence is much lower at 0.05%.

Screening for factor V Leiden is not recommended, even after a venous thromboembolism. The logic behind this is that a previous thromboembolism itself is a risk factor for further events and this should dictate specific management in the future, rather than the particular thrombophilia identified.

The table below shows the prevalence and relative risk of venous thromboembolism (VTE) of the different inherited thrombophilias:

| Condition | Prevalence | Relative risk of VTE |
|---|---|---|
| Factor V Leiden (heterozygous) | 5% | 4 |
| Factor V Leiden (homozygous) | 0.05% | 10 |
| Prothrombin gene mutation (heterozygous) | 1.5% | 3 |
| Protein C deficiency | 0.3% | 10 |

| Condition | Prevalence | Relative risk of VTE |
|---|---|---|
| Protein S deficiency | 0.1% | 5-10 |
| Antithrombin III deficiency | 0.02 | 10-20 |

# ANTITHROMBIN III DEFICIENCY

Antithrombin III deficiency is an inherited cause of thrombophilia occurring in approximately 1:3,000 of the population. Inheritance is autosomal dominant.

Antithrombin III inhibits several clotting factors, primarily thrombin, factor X and factor IX. It mediates the effects of heparin

Antithrombin III deficiency comprises a heterogeneous group of disorders, with some patients having a deficiency of normal antithrombin III whilst others produce abnormal antithrombin III

Features
recurrent venous thromboses
arterial thromboses do occur but are uncommon

Management
thromboembolic events are treated with lifelong warfarinisation
heparinisation during pregnancy*
antithrombin III concentrates (often using during surgery or childbirth)

The table below shows the prevalence and relative risk of venous thromboembolism (VTE) of the different inherited thrombophilias:

# PROTEIN C DEFICIENCY

Protein C deficiency is an autosomal codominant condition which causes an increased risk of thrombosis

Features

- venous thromboembolism
- skin necrosis following the commencement of warfarin: when warfarin is first started biosynthesis of protein C is reduced. This results in a temporary procoagulant state after initially starting warfarin, normally avoided by concurrent heparin administration. Thrombosis may occur in venules leading to skin necrosis

# GRANULOCYTE-COLONY STIMULATING FACTORS

Recombinant human granulocyte-colony stimulating factors are used to increase neutrophil counts in patients who are neutropenic secondary to chemotherapy or other factors.

Examples include:

- filgrastim
- perfilgrastim

# PRIMARY IMMUNODEFICIENCY

Primary immunodeficiency disorders may be classified according to which component of the immune system they affect.

### Neutrophil disorders

| Disorder | Underlying defect | Notes |
|---|---|---|
| Chronic granulomatous disease | Lack of NADPH oxidase reduces ability of phagocytes to produce reactive oxygen species | Causes recurrent pneumonias and abscesses, particularly due to catalase-positive bacteria (e.g. *Staphylococcus aureus* and fungi (e.g. *Aspergillus*)<br>Negative nitroblue-tetrazolium test<br>Abnormal dihydrorhodamine flow cytometry test |
| Chediak-Higashi syndrome | Microtubule polymerization defect which leads to a decrease in phagocytosis | Affected children have 'partial albinism' and peripheral neuropathy. Recurrent bacterial infections are seen<br>Giant granules in neutrophils and platelets |
| Leukocyte adhesion deficiency | Defect of LFA-1 integrin (CD18) protein on neutrophils | Recurrent bacterial infections.<br>Delay in umbilical cord sloughing may be seen<br>Absence of neutrophils/pus at sites of infection |

### B-cell disorders

| Disorder | Underlying defect | Notes |
|---|---|---|
| Common variable immunodeficiency | Many varying causes | Hypogammaglobulinemia is seen. May predispose to autoimmune disorders and lymphona |
| Bruton's (x-linked) congenital agammaglobulinaemia | Defect in Bruton's tyrosine kinase (BTK) gene that leads to a severe block in B cell development | X-linked recessive. Recurrent bacterial infections are seen<br>Absence of B-cells with reduced immunoglogulins of all classes |
| Selective immunoglobulin A deficiency | Maturation defect in B cells | Most common primary antibody deficiency. Recurrent sinus and respiratory infections<br><br>Associated with coeliac disease and may cause false negative coeliac antibody screen<br><br>Severe reactions to blood transfusions may occur (anti-IgA antibodies → analphylaxis) |

### T-cell disorders

| Disorder | Underlying defect | Notes |
|---|---|---|
| DiGeorge syndrome | 22q11.2 deletion, failure to develop 3rd and 4th pharyngeal pouches | Common features include congenital heart disease (e.g. tetralogy of Fallot), learning difficulties, hypocalcaemia, recurrent viral/fungal diseases, cleft palate |

### Combined B- and T-cell disorders

| Disorder | Underlying defect | Notes |
|---|---|---|
| Severe combined immunodeficiency | Many varying causes. Most common (X-linked) due to defect in the common gamma chain, a protein used in the receptors for IL-2 and other interleukins. Other causes include adenosine deaminase deficiency | Recurrent infections due to viruses, bacteria and fungi.<br>Reduced T-cell receptor excision circles<br>Stem cell transplantation may be successful |
| Ataxic telangiectasia | Defect in DNA repair enzymes | Autosomal recessive. Features include cerebellar ataxia, telangiectasia (spider angiomas), recurrent chest infections and 10% risk of developing malignancy, lymphoma or leukaemia |
| Wiskott-Aldrich syndrome | Defect in WASP gene | X-linked recessive. Features include recurrent bacterial infections, eczema, thrombocytopaenia.<br>Low IgM levels<br>Increased risk of autoimmune disorders and malignancy |
| Hyper IgM Syndromes | Mutations in the CD40 gene | Infection/Pneumocystis pneumonia, hepatitis, diarrhoea |

# WISKOTT-ALDRICH SYNDROME

Wiskott-Aldrich syndrome causes primary immunodeficiency due to a combined B- and T-cell dysfunction. It is inherited in a X-linked recessive fashion and is thought to be caused by mutation in the WASP gene.

Features

- recurrent bacterial infections (e.g. Chest)
- eczema
- thrombocytopaenia
- low IgM levels

# HAEMATOLOGICAL MALIGNANCIES: GENETICS

Below is a brief summary of the common translocations associated with haematological malignancies

t(9;22) - Philadelphia chromosome

- present in > 95% of patients with CML
- this results in part of the Abelson proto-oncogene being moved to the BCR gene on chromosome 22
- the resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal
- poor prognostic indicator in ALL

t(15;17)

- seen in acute promyelocytic leukaemia (M3)
- fusion of PML and RAR-alpha genes

t(8;14)

- seen in Burkitt's lymphoma
- MYC oncogene is translocated to an immunoglobulin gene

t(11;14)

- Mantle cell lymphoma
- deregulation of the cyclin D1 (BCL-1) gene

t(14;18)

- follicular lymphoma
- increased BCL-2 transcription

# HAEMATOLOGICAL MALIGNANCIES: INFECTIONS

Viruses

- EBV: Hodgkin's and Burkitt's lymphoma, nasopharyngeal carcinoma
- HTLV-1: Adult T-cell leukaemia/lymphoma
- HIV-1: High-grade B-cell lymphoma

Bacteria

- Helicobacter pylori: gastric lymphoma (MALT)

Protozoa

- malaria: Burkitt's lymphoma

# LEUKAEMOID REACTION

The leukaemoid reaction describes the presence of immature cells such as myeloblasts, promyelocytes and nucleated red cells in the peripheral blood. This may be due to infiltration of the bone marrow causing the immature cells to be 'pushed out' or sudden demand for new cells

Causes
- severe infection
- severe haemolysis
- massive haemorrhage
- metastatic cancer with bone marrow infiltration

A relatively common clinical problem is differentiating chronic myeloid leukaemia from a leukaemoid reaction. The following differences may help:

Leukaemoid reaction
- high leucocyte alkaline phosphatase score
- toxic granulation (Dohle bodies) in the white cells
- 'left shift' of neutrophils i.e. three or fewer segments of the nucleus

Chronic myeloid leukaemia
- low leucocyte alkaline phosphatase score

# ACUTE LYMPHOBLASTIC LEUKAEMIA: PROGNOSTIC FEATURES

Acute lymphoblastic leukaemia is malignancy of lymphoid progenitor cells affecting B or T cell lineage resulting in arresting of lymphoid cell maturation and proliferation of immature blast (lymphoblast) cells that leads to bone marrow and tissue infiltration.

Basics
- most common childhood cancer
- peak age = 2-5yrs
- 80% of childhood leukaemia

Good prognostic factors
- French-American-British (FAB) L1 type
- common ALL
- pre-B phenotype
- low initial WBC
- del(9p)

Poor prognostic factors

- FAB L3 type
- T or B cell surface markers
- Philadelphia translocation, t(9;22)
- age < 2 years or > 10 years
- male sex
- CNS involvement
- high initial WBC (e.g. > 100 * 109/l)
- non-Caucasian

# ACUTE MYELOID LEUKAEMIA

Acute myeloid leukaemia is the more common form of acute leukaemia in adults. It may occur as a primary disease or following a secondary transformation of a myeloproliferative disorder.

Features are largely related to bone marrow failure:

- anaemia: pallor, lethargy, weakness
- neutropenia: whilst white cell counts may be very high, functioning neutrophil levels may be low leading to frequent infections etc
- thrombocytopenia: bleeding
- splenomegaly
- bone pain

Poor prognostic features

- > 60 years
- > 20% blasts after first course of chemo
- cytogenetics: deletions of chromosome 5 or 7

Acute promyelocytic leukaemia M3

- associated with t(15;17)
- fusion of PML and RAR-alpha genes
- presents younger than other types of AML (average = 25 years old)
- Auer rods (seen with myeloperoxidase stain)
- DIC or thrombocytopenia often at presentation
- good prognosis

Classification - French-American-British (FAB)

- MO - undifferentiated
- M1 - without maturation
- M2 - with granulocytic maturation
- M3 - acute promyelocytic

- M4 - granulocytic and monocytic maturation
- M5 - monocytic
- M6 - erythroleukaemia
- M7 - megakaryoblastic

# ACUTE PROMYELOCYTIC LEUKAEMIA

You are not normally expected to be able to differentiate the different subtypes of acute myeloid leukaemia (AML) for the MRCP. An exception to this is acute promyelocytic leukaemia (APML, the M3 subtype of AML). The importance of identifying APML lies in both the presentation (classically disseminated intravascular coagulation) and management

APML is associated with the t(15;17) translocation which causes fusion of the PML and RAR-alpha genes.

Features
- presents younger than other types of AML (average = 25 years old)
- DIC or thrombocytopenia often at presentation
- good prognosis

# CHRONIC LYMPHOCYTIC LEUKAEMIA

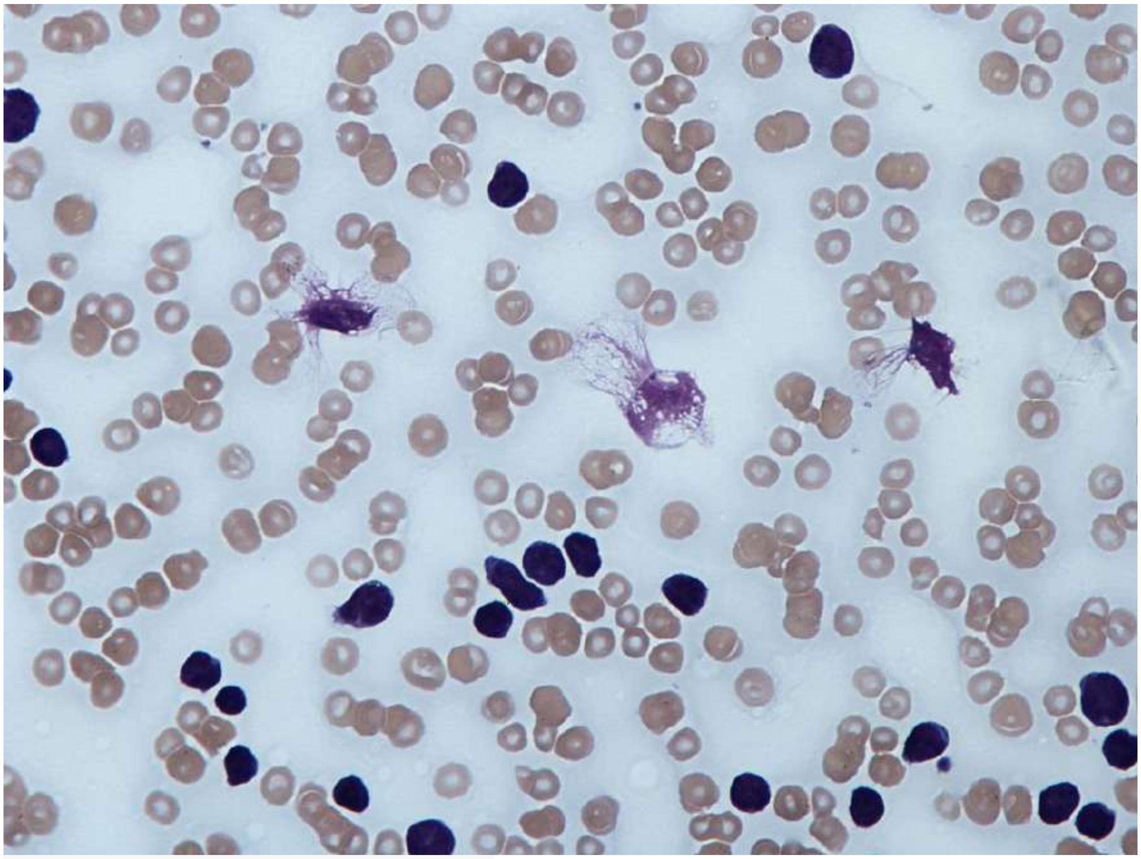
Chronic lymphocytic leukaemia (CLL) is caused by a monoclonal proliferation of well-differentiated lymphocytes which are almost always B-cells (99%). It is the most common form of leukaemia seen in adults.

Features
- often none
- constitutional: anorexia, weight loss
- bleeding, infections
- lymphadenopathy more marked than CML

Complications
- anaemia
- hypogammaglobulinaemia leading to recurrent infections
- warm autoimmune haemolytic anaemia in 10-15% of patients
- transformation to high-grade lymphoma (Richter's transformation)

Investigations
- blood film: smudge cells (also known as smear cells)

- immunophenotyping



Peripheral blood film showing smudge B cells

# CHRONIC LYMPHOCYTIC LEUKAEMIA: MANAGEMENT

Indications for treatment

- progressive marrow failure: the development or worsening of anaemia and/or thrombocytopenia
- massive (>10 cm) or progressive lymphadenopathy
- massive (>6 cm) or progressive splenomegaly
- progressive lymphocytosis: > 50% increase over 2 months or lymphocyte doubling time < 6 months
- systemic symptoms: weight loss > 10% in previous 6 months, fever >38ºC for > 2 weeks, extreme fatigue, night sweats
- autoimmune cytopaenias e.g. ITP

Management

- patients who have no indications for treatment are monitored with regular blood counts
- fludarabine, cyclophosphamide and rituximab (FCR) has now emerged as the initial treatment of choice for the majority of patients
- ibrutinib may be used in patients who have failed a previous therapy

# CHRONIC LYMPHOCYTIC LEUKAEMIA: PROGNOSTIC FACTORS

Poor prognostic factors (median survival 3-5 years)

- male sex
- age > 70 years
- lymphocyte count > 50
- prolymphocytes comprising more than 10% of blood lymphocytes
- lymphocyte doubling time < 12 months
- raised LDH
- CD38 expression positive
- TP53 mutation

Chromosomal changes

- deletion of the long arm of chromosome 13 (del 13q) is the most common abnormality, being seen in around 50% of patients. It is associated with a **good** prognosis
- deletions of part of the short arm of chromosome 17 (del 17p) are seen in around 5-10% of patients and are associated with a **poor** prognosis

# CHRONIC MYELOID LEUKAEMIA

The Philadelphia chromosome is present in more than 95% of patients with chronic myeloid leukaemia (CML). It is due to a translocation between the long arm of chromosome 9 and 22 - t(9:22)(q34; q11). This results in part of the ABL proto-oncogene from chromosome 9 being fused with the BCR gene from chromosome 22. The resulting BCR-ABL gene codes for a fusion protein which has tyrosine kinase activity in excess of normal

Presentation (60-70 years)

- anaemia: lethargy
- weight loss and sweating are common
- splenomegaly may be marked → abdo discomfort
- an increase in granulocytes at different stages of maturation +/- thrombocytosis
- decreased leukocyte alkaline phosphatase
- may undergo blast transformation (AML in 80%, ALL in 20%)

Management

- imatinib is now considered first-line treatment
- hydroxyurea
- interferon-alpha
- allogenic bone marrow transplant

Imatinib

- inhibitor of the tyrosine kinase associated with the BCR-ABL defect
- very high response rate in chronic phase CML

# HODGKIN'S LYMPHOMA

Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterised by the presence of the Reed-Sternberg cell. It has a bimodal age distributions being most common in the third and seventh decades

Features
- lymphadenopathy (75%) - painless, non-tender, asymmetrical
- systemic (25%): weight loss, pruritus, night sweats, fever (Pel-Ebstein)
- alcohol pain in HL
- normocytic anaemia, eosinophilia
- LDH raised

# HODGKIN'S LYMPHOMA: HISTOLOGICAL CLASSIFICATION AND PROGNOSIS

Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterised by the presence of the Reed-Sternberg cell. It has a bimodal age distributions being most common in the third and seventh decades

Histological classification

| Type | Frequency | Prognosis | Notes |
|---|---|---|---|
| Nodular sclerosing | Most common (around 70%) | Good prognosis | More common in women. Associated with lacunar cells |
| Mixed cellularity | Around 20% | Good prognosis | Associated with a large number of Reed-Sternberg cells |
| Lymphocyte predominant | A*round 5% | Best prognosis | |
| Lymphocyte depleted | Rare | Worst prognosis | |

'B' symptoms also imply a poor prognosis
- weight loss > 10% in last 6 months
- fever > 38ºC
- night sweats

Other factors associated with a poor prognosis identified in a 1998 NEJM paper included:
- age > 45 years
- stage IV disease
- haemoglobin < 10.5 g/dl

- lymphocyte count < 600/µl or < 8%
- male
- albumin < 40 g/l
- white blood count > 15,000/µl

*Reed-Sternberg cells with nuclei surrounded by a clear space

# HODGKIN'S LYMPHOMA: STAGING

Hodgkin's lymphoma is a malignant proliferation of lymphocytes characterised by the presence of the Reed-Sternberg cell. It has a bimodal age distributions being most common in the third and seventh decades

Ann-Arbor staging of Hodgkin's lymphoma
I: single lymph node
II: 2 or more lymph nodes/regions on same side of diaphragm
III: nodes on both sides of diaphragm
IV: spread beyond lymph nodes

Each stage may be subdivided into A or B
A = no systemic symptoms other than pruritus
B = weight loss > 10% in last 6 months, fever > 38c, night sweats (poor prognosis)

# NON-HODGKIN'S LYMPHOMA

Lymphoma is the malignant proliferation of lymphocytes which accumulate in lymph nodes or other organs. Lymphoma may be classified as either Hodgkin's lymphoma (a specific type of lymphoma characterized by the presence of Reed-Sternberg cells) or non-Hodgkin's lymphoma (every other type of lymphoma that is not Hodgkin's lymphoma). Non-Hodgkin's lymphoma is the 6th most common cause of cancer in the UK. Non-Hodgkin's lymphoma may affect either B or T-cells and can be further classified as high grade or low grade.

Epidemiology
- Non-Hodgkin's lymphoma is much more common than Hodgkin's lymphoma
- While different subtypes can affect different ages, it typically affects the elderly with one-third of cases occurring in those over 75 years of age
- The incidence rate is 28 for men and 20 for females per 100,000 of the population

Risk factors
- Elderly
- Caucasians

- History of viral infection (specifically Epstein-Barr virus)
- Family history
- Certain chemical agents (pesticides, solvents)
- History of chemotherapy or radiotherapy
- Immunodeficiency (transplant, HIV, diabetes mellitus)
- Autoimmune disease (SLE, Sjogren's, coeliac disease)

Symptoms

- Painless lymphadenopathy (non-tender, rubbery, asymmetrical)
- Constitutional/B symptoms (fever, weight loss, night sweats, lethargy)
- Extranodal Disease - gastric (dyspepsia, dysphagia, weight loss, abdominal pain), bone marrow (pancytopenia, bone pain), lungs, skin, central nervous system (nerve palsies)

While differentiating Hodgkin's lymphoma from non-Hodgkin's lymphoma is done by biopsy certain elements of the clinical presentation can help point towards one rather than the other.

- Lymphadenopathy in Hodgkin's lymphoma can experience alcohol-induced pain in the node
- 'B' symptoms typically occur earlier in Hodgkin's lymphoma and later in non-Hodgkin's lymphoma
- Extra-nodal disease is much more common in non-Hodgkin's lymphoma than in Hodgkin's lymphoma

Signs

- Signs of weight loss
- Lymphadenopathy (typically in the cervical, axillary or inguinal region)
- Palpable abdominal mass - hepatomegaly, splenomegaly, lymph nodes
- Testicular mass
- Fever

Investigations

- Excisional node biopsy is the diagnostic investigation of choice (certain subtypes will have a classical appearance on biopsy such as Burkitt's lymphoma having a 'starry sky' appearance)
- CT chest, abdomen and pelvis (to assess staging)
- HIV test (often performed as this is a risk factor for non-Hodgkin's lymphoma)
- FBC and blood film (patient may have a normocytic anaemia and can help rule out other haematological malignancy such as leukaemia)
- ESR (useful as a prognostic indicator)
- LDH (a marker of cell turnover, useful as a prognostic indicator)
- Other investigations can be ordered as the clinical picture indicates (LFT's if liver metastasis suspected, PET CT or bone marrow biopsy to look for bone involvement, LP if neurological symptoms)

Staging

- The most common staging system used for non-Hodgkin's lymphoma is the Ann Arbor system.

- → Stage 1 - One node affected
- → Stage 2 - More than one node affected on the same side of the diaphragm
- → Stage 3 - One node affected on either side of the diaphragm
- → Stage 4 - Extra-nodal involvement e.g. Spleen, bone marrow or CNS
- The stage is combined with the letter A or B to indicate the presence of 'B' symptoms. With the letter A indicating no B symptoms present and B indicating any of the beta symptoms present. For example, a patient with a single node affected and no 'B' symptoms would be stage 1A.

Management
- Management is dependent on the specific sub-type of non-Hodgkin's lymphoma and will typically take the form of watchful waiting, chemotherapy or radiotherapy.
- All patients will receive flu/pneumococcal vaccines
- Patients with neutropenia may require antibiotic prophylaxis

Complications
- Bone marrow infiltration causing anaemia, neutropenia or thrombocytopenia
- Superior vena cava obstruction
- Metastasis
- Spinal cord compression
- Complications related to treatment e.g. Side effects of chemotherapy

Prognosis
- Low-grade non-Hodgkin's lymphoma has a better prognosis
- High-grade non-Hodgkin's lymphoma has a worse prognosis but a higher cure rate

# BURKITT'S LYMPHOMA

Burkitt's lymphoma is a high-grade B-cell neoplasm. There are two major forms:
- endemic (African) form: typically involves maxilla or mandible
- sporadic form: abdominal (e.g. ileo-caecal) tumours are the most common form. More common in patients with HIV

Burkitt's lymphoma is associated with the c-myc gene translocation, usually t(8:14). The Epstein-Barr virus (EBV) is strongly implicated in the development of the African form of Burkitt's lymphoma and to a lesser extent the sporadic form.

Microscopy findings
- 'starry sky' appearance: lymphocyte sheets interspersed with macrophages containing dead apoptotic tumour cells

Management is with chemotherapy. This tends to produce a rapid response which may cause 'tumour lysis syndrome'. Rasburicase (a recombinant version of urate oxidase, an enzyme which catalyses the conversion of uric acid to allantoin*) is often given before the chemotherapy to reduce the risk of this occurring. Complications of tumour lysis syndrome include:

- hyperkalaemia
- hyperphosphataemia
- hypocalcaemia
- hyperuricaemia
- acute renal failure

*allantoin is 5-10 times more soluble than uric acid, so renal excretion is more effective

# HAIRY CELL LEUKAEMIA

Hairy cell leukaemia is a rare malignant proliferation disorder of B cells. It is more common in males (4:1)

Features

- pancytopenia
- splenomegaly
- skin vasculitis in 1/3 patients
- 'dry tap' despite bone marrow hypercellularity
- tartrate resistant acid phosphotase (TRAP) stain positive

Management

- chemotherapy is first-line: cladribine, pentostatin
- immunotherapy is second-line: rituximab, interferon-alpha

# MANTLE CELL LYMPHOMA

Overview

- type of B-cell lymphoma

Genetics

- CD5+, CD19+, CD22+, CD23-, CD10-
- associated translocation (11;14) causing over-expression of the cyclin D1 (BCL-1) gene

Features

- widespread lymphadenopathy
- poor prognosis

# WALDENSTROM'S MACROGLOBULINAEMIA

Waldenstrom's macroglobulinaemia is an uncommon condition seen in older men. It is a lymphoplasmacytoid malignancy characterised by the secretion of a monoclonal IgM paraprotein

Features
- monoclonal IgM paraproteinaemia
- systemic upset: weight loss, lethargy
- hyperviscosity syndrome e.g. visual disturbance
  - the pentameric configuration of IgM increases serum viscosity
- hepatosplenomegaly
- lymphadenopathy
- cryoglobulinaemia e.g. Raynaud's

# LYMPHADENOPATHY

There are many causes of generalised lymphadenopathy

Infective
- infectious mononucleosis
- HIV, including seroconversion illness
- eczema with secondary infection
- rubella
- toxoplasmosis
- CMV
- tuberculosis
- roseola infantum

Neoplastic
- leukaemia
- lymphoma

Others
- autoimmune conditions: SLE, rheumatoid arthritis
- graft versus host disease
- sarcoidosis
- drugs: phenytoin and to a lesser extent allopurinol, isoniazid

# TUMOUR LYSIS SYNDROME

Tumour lysis syndrome (TLS) is a potentially deadly condition related to the treatment of high-grade lymphomas and leukaemias. It can occur in the absence of chemotherapy but is usually triggered by the introduction of combination chemotherapy. On occasion, it can occur with steroid treatment alone. Awareness of the condition is critical as prophylactic medication can be given to prevent the potentially deadly effects of tumour cell lysis.

Patients at high risk of TLS should be given IV allopurinol or IV rasburicase immediately prior to and during the first days of chemotherapy. Rasburicase is a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin. Allantoin is much more water-soluble than uric acid and is, therefore, more easily excreted by the kidneys. Patients in lower-risk groups should be given oral allopurinol during chemotherapy cycles in an attempt to avoid the condition. Rasburicase and allopurinol should not be given together in the management of tumour lysis syndrome as this reduces the effect of rasburicase.

TLS occurs from the breakdown of the tumour cells and the subsequent release of chemicals from the cell. It leads to a high potassium and high phosphate level in the presence of a low calcium. It should be suspected in any patient presenting with an acute kidney injury in the presence of a high phosphate and high uric acid level.

From 2004 TLS has been graded using the Cairo-Bishop scoring system -
Laboratory tumor lysis syndrome: abnormality in two or more of the following, occurring within three days before or seven days after chemotherapy.

- uric acid > 475umol/l or 25% increase
- potassium > 6 mmol/l or 25% increase
- phosphate > 1.125mmol/l or 25% increase
- calcium < 1.75mmol/l or 25% decrease

Clinical tumor lysis syndrome: laboratory tumour lysis syndrome plus one or more of the following:

- increased serum creatinine (1.5 times upper limit of normal)
- cardiac arrhythmia or sudden death
- seizure

# CARCINOGENS

| Carcinogen | Cancer |
|---|---|
| Aflatoxin (produced by *Aspergillus*) | Liver - (hepatocellular carcinoma) |
| Aniline dyes | Bladder (transitional cell carcinoma) |
| Asbestos | Mesothelioma and bronchial carcinoma |
| Nitrosamines | Oesophageal and gastric cancer |
| Vinyl chloride | Hepatic angiosarcoma |

# GENETICS AND SURGICAL DISEASE

Some of the more commonly occurring genetic conditions occurring in surgical patients are presented here.

Li-Fraumeni Syndrome

- Autosomal dominant
- Consists of germline mutations to p53 tumour suppressor gene
- High incidence of malignancies particularly sarcomas and leukaemias
- Diagnosed when:

*Individual develops sarcoma under 45 years
*First degree relative diagnosed with any cancer below age 45 years and another family member develops malignancy under 45 years or sarcoma at any age

**BRCA 1 and 2**

- Carried on chromosome 17 (BRCA 1) and Chromosome 13 (BRCA 2)
- Linked to developing breast cancer (60%) risk.
- Associated risk of developing ovarian cancer (55% with BRCA 1 and 25% with BRCA 2).
- BRCA2 mutation is associated with prostate cancer in men

**Lynch Syndrome**

- Autosomal dominant
- Develop colonic cancer and endometrial cancer at young age
- 80% of affected individuals will get colonic and/ or endometrial cancer
- High risk individuals may be identified using the Amsterdam criteria

**Amsterdam criteria**

- Three or more family members with a confirmed diagnosis of colorectal cancer, one of whom is a first degree (parent, child, sibling) relative of the other two.
- Two successive affected generations.
- One or more colon cancers diagnosed under age 50 years.

- Familial adenomatous polyposis (FAP) has been excluded.

**Gardners syndrome**

- Autosomal dominant familial colorectal polyposis
- Multiple colonic polyps
- Extra colonic diseases include: skull osteoma, thyroid cancer and epidermoid cysts
- Desmoid tumours are seen in 15%
- Mutation of APC gene located on chromosome 5
- Due to colonic polyps most patients will undergo colectomy to reduce risk of colorectal cancer
- Now considered a variant of familial adenomatous polyposis coli

# TUMOUR MARKERS

Tumour markers may be divided into:

- monoclonal antibodies against carbohydrate or glycoprotein tumour antigens
- tumour antigens
- enzymes (alkaline phosphatase, neurone specific enolase)
- hormones (e.g. calcitonin, ADH)

It should be noted that tumour markers usually have a low specificity

## Monoclonal antibodies

| Tumour marker | Association |
|---|---|
| CA 125 | Ovarian cancer |
| CA 19-9 | Pancreatic cancer |
| CA 15-3 | Breast cancer |

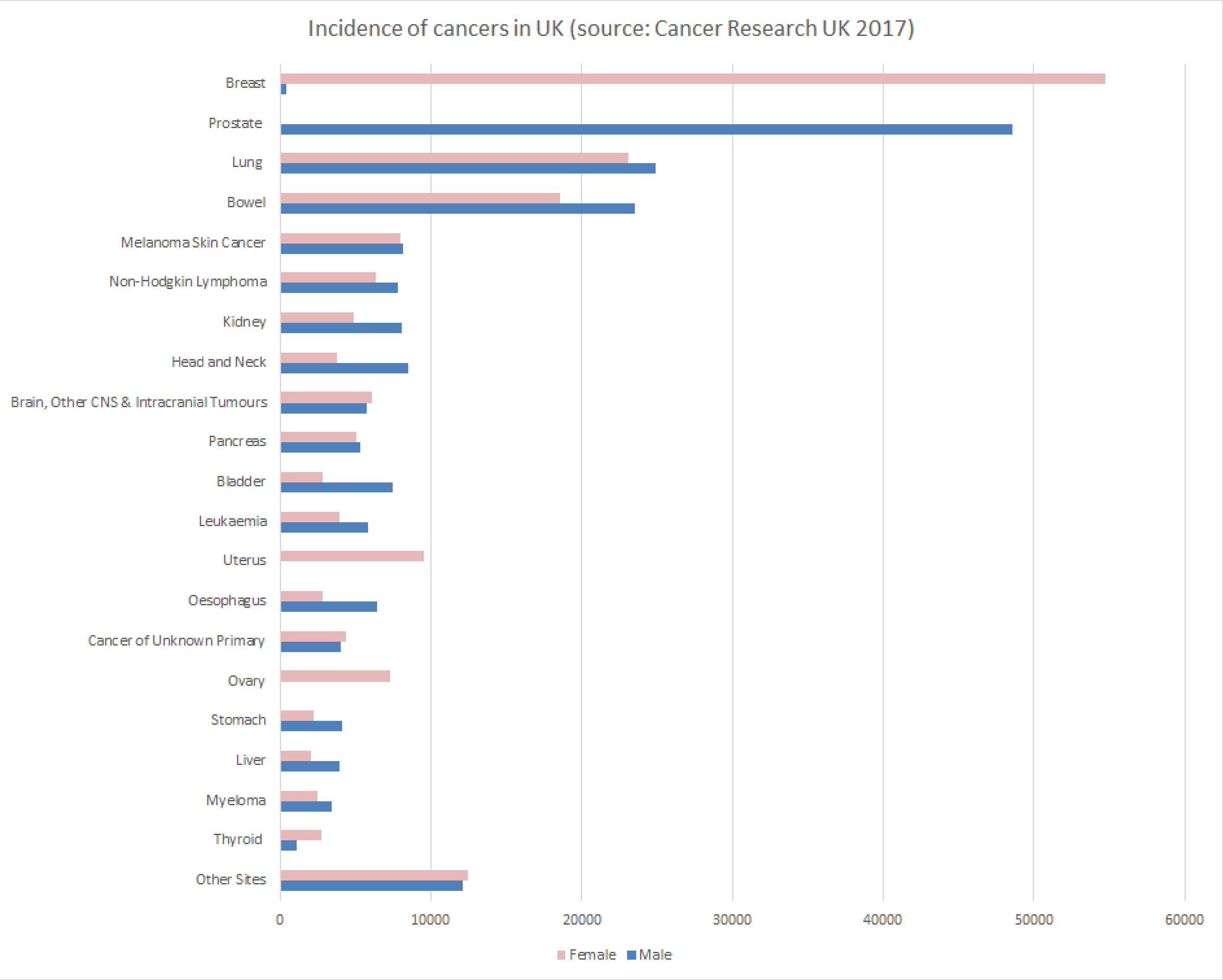
## Tumour antigens

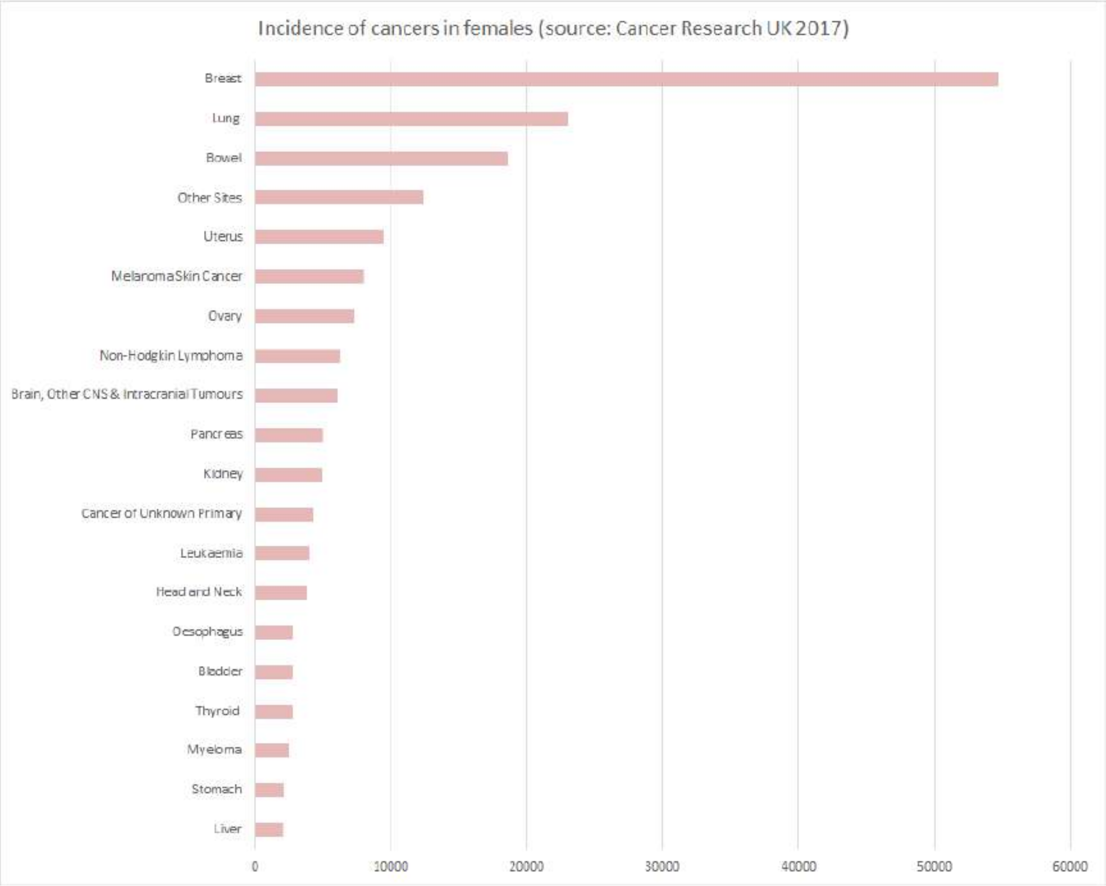
| Tumour marker | Association |
|---|---|
| Prostate specific antigen (PSA) | Prostatic carcinoma |
| Alpha-feto protein (AFP) | Hepatocellular carcinoma, teratoma |
| Carcinoembryonic antigen (CEA) | Colorectal cancer |
| S-100 | Melanoma, schwannomas |
| Bombesin | Small cell lung carcinoma, gastric cancer, neuroblastoma |

# CANCER IN THE UK

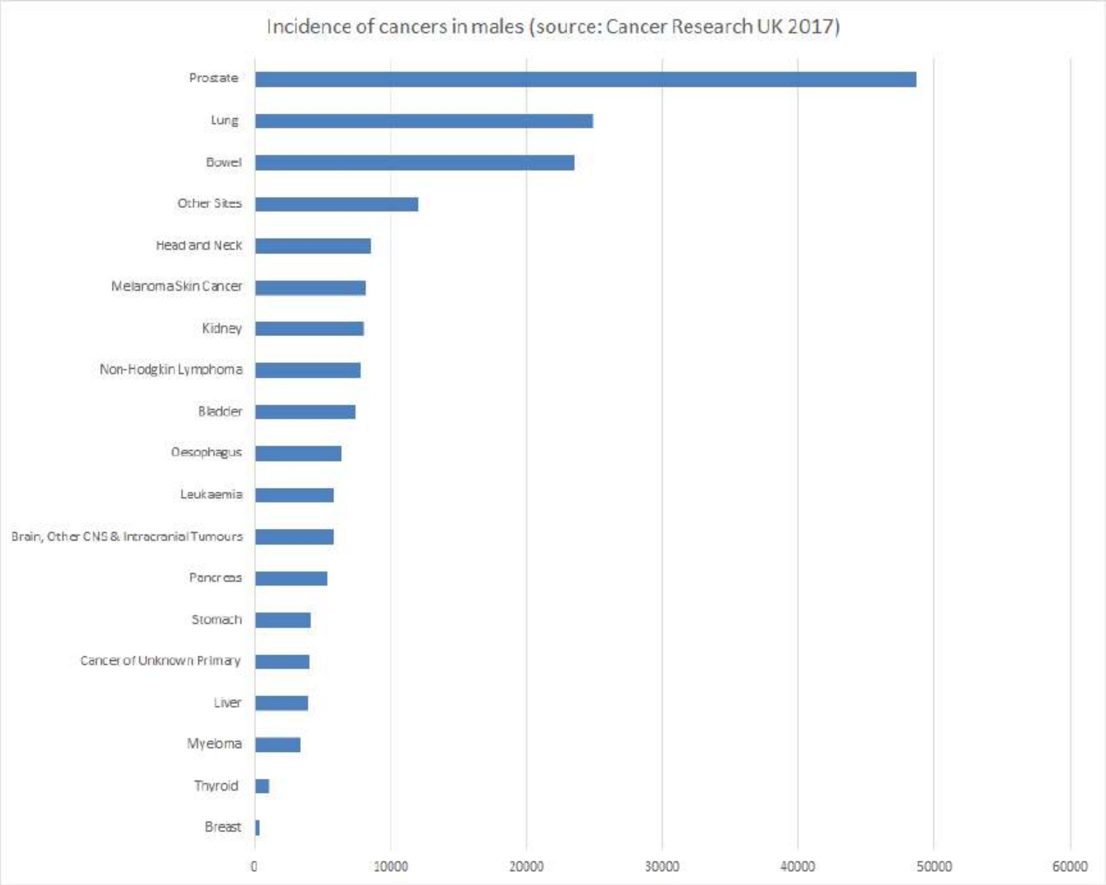
The most common causes of cancer in the UK are as follows*

1. Breast
2. Lung
3. Colorectal
4. Prostate
5. Bladder
6. Non-Hodgkin's lymphoma
7. Melanoma
8. Stomach
9. Oesophagus
10. Pancreas





Incidence of cancers in females (source: Cancer Research UK 2017)



Incidence of cancers in males (source: Cancer Research UK 2017)

The most common causes of death from cancer in the UK are as follows:
1. Lung
2. Colorectal
3. Breast
4. Prostate
5. Pancreas
6. Oesophagus
7. Stomach
8. Bladder
9. Non-Hodgkin's lymphoma
10. Ovarian

*excludes non-melanoma skin cancer

# LUNG CANCER: NON-SMALL CELL

There are three main subtypes of non-small cell lung cancer:

Squamous cell cancer
- typically central
- associated with parathyroid hormone-related protein (PTHrP) secretion → hypercalcaemia
- strongly associated with finger clubbing
- hypertrophic pulmonary osteoarthropathy (HPOA)

Adenocarcinoma
- typically peripheral
- most common type of lung cancer in non-smokers, although the majority of patients who develop lung adenocarcinoma are smokers

Large cell lung carcinoma
- typically peripheral
- anaplastic, poorly differentiated tumours with a poor prognosis
- may secrete β-hCG

# BREAST CANCER: RISK FACTORS

Predisposing factors
- BRCA1, BRCA2 genes - 40% lifetime risk of breast/ovarian cancer
- 1st degree relative premenopausal relative with breast cancer (e.g. mother)
- nulliparity, 1st pregnancy > 30 yrs (twice risk of women having 1st child < 25 yrs)
- early menarche, late menopause
- combined hormone replacement therapy (relative risk increase * 1.023/year of use), combined oral contraceptive use
- past breast cancer
- not breastfeeding
- ionising radiation
- p53 gene mutations
- obesity
- previous surgery for benign disease (?more follow-up, scar hides lump)

# ANTI-OESTROGEN DRUGS

## Selective oEstrogen Receptor Modulators (SERM)

Tamoxifen is a SERM which acts as an oestrogen receptor antagonist and partial agonist. It is used in the management of oestrogen receptor-positive breast cancer.

Adverse effects

- menstrual disturbance: vaginal bleeding, amenorrhoea
- hot flushes - 3% of patients stop taking tamoxifen due to climacteric side-effects
- venous thromboembolism
- endometrial cancer
- osteoporosis

## Aromatase inhibitors

Anastrozole and letrozole are aromatase inhibitors that reduces peripheral oestrogen synthesis. This is important as aromatisation accounts for the majority of oestrogen production in postmenopausal women and therefore anastrozole is used for ER +ve breast cancer in this group.

Adverse effects

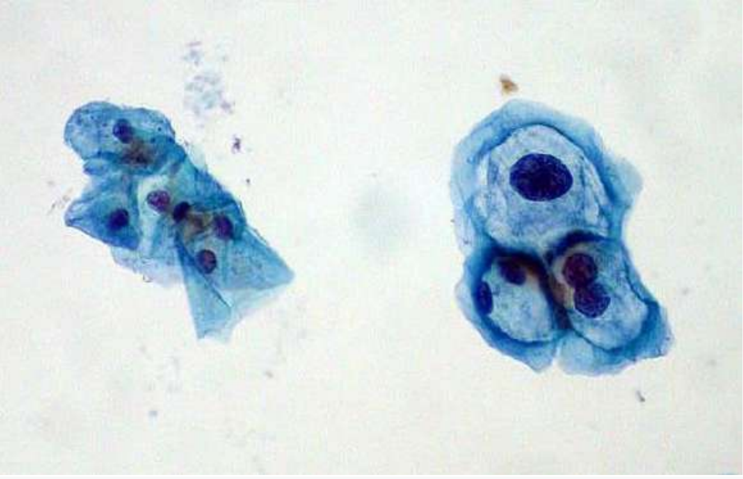
- osteoporosis
    - NICE recommends a DEXA scan when initiating a patient on aromatase inhibitors for breast cancer
- hot flushes
- arthralgia, myalgia
- insomnia

# CERVICAL CANCER: HUMAN PAPILLOMA VIRUS INFECTION

Human papilloma virus (HPV) infection is the most important risk factor for developing cervical cancer. Subtypes 16,18 & 33 are particularly carcinogenic. The other most common subtypes (6 & 11) are non-carcinogenic and associated with genital warts.

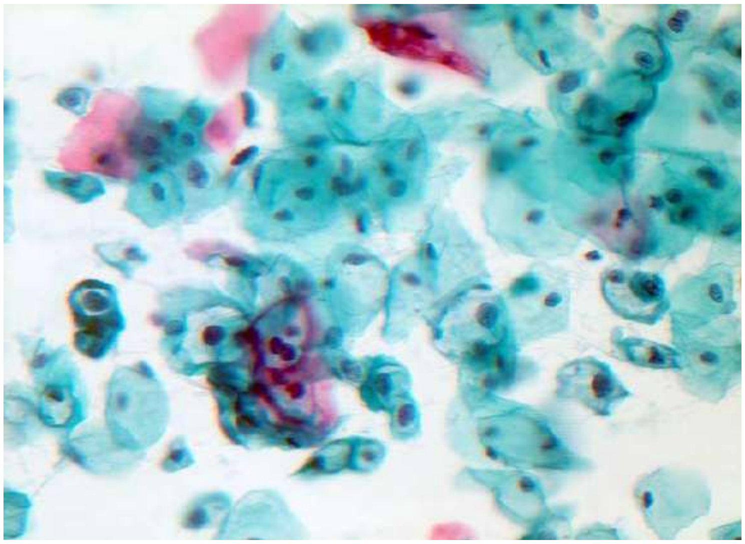
Infected endocervical cells may undergo changes resulting in the development of koilocytes. These have the following characteristics:

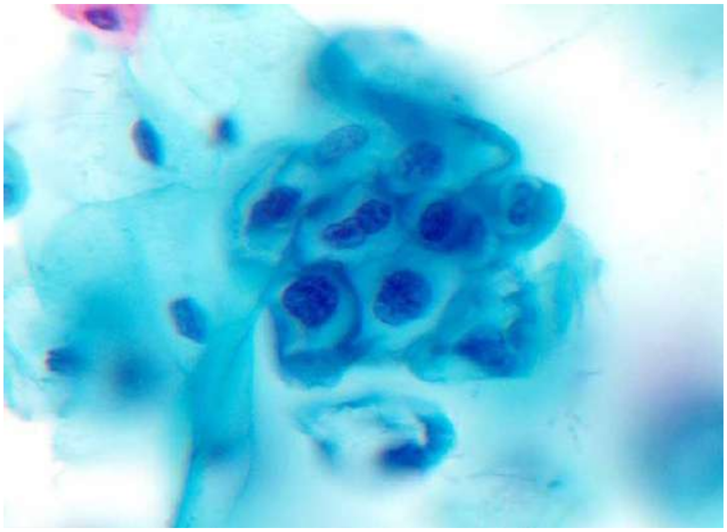
- enlarged nucleus
- irregular nuclear membrane contour
- the nucleus stains darker than normal (hyperchromasia)
- a perinuclear halo may be seen



Pap smear with a group of normal cervical cells on the left and HPV-infected cells showing features typical of koilocytes on the right

Some other examples of koilocytes are shown below:





# MYELOMA: FEATURES

Multiple myeloma is a neoplasm of the bone marrow plasma cells. The peak incidence is patients aged 60-70 years.

Clinical features

- bone disease: bone pain, osteoporosis + pathological fractures (typically vertebral), osteolytic lesions
- lethargy
- infection
- hypercalcaemia (see below)
- renal failure
- other features: amyloidosis e.g. Macroglossia, carpal tunnel syndrome; neuropathy; hyperviscosity

Investigations

- monoclonal proteins (usually IgG or IgA) in the serum and urine (Bence Jones proteins)
- increased plasma cells in the bone marrow
- historically a skeletal survey has been done to look for bone lesions. However, whole-body MRI is increasingly used and is now recommended in the 2016 NICE guidelines
- X-rays: 'rain-drop skull' (likened to the pattern rain forms after hitting a surface and splashing, where it leaves a random pattern of dark spots). Note that a very similar, but subtly different finding is found in primary hyperparathyroidism - 'pepperpot skull'

The diagnostic criteria for multiple myeloma requires one major and one minor criteria or three minor criteria in an individual who has signs or symptoms of multiple myeloma.

Major criteria

- Plasmacytoma (as demonstrated on evaluation of biopsy specimen)
- 30% plasma cells in a bone marrow sample
- Elevated levels of M protein in the blood or urine

Minor criteria

- 10% to 30% plasma cells in a bone marrow sample.
- Minor elevations in the level of M protein in the blood or urine.
- Osteolytic lesions (as demonstrated on imaging studies).
- Low levels of antibodies (not produced by the cancer cells) in the blood.

Hypercalcaemia in myeloma

- primary factor: due primarily to increased osteoclastic bone resorption caused by local cytokines (e.g. IL-1, tumour necrosis factor) released by the myeloma cells
- much less common contributing factors: impaired renal function, increased renal tubular calcium reabsorption and elevated PTH-rP levels

# MYELOMA: PROGNOSIS

B2-microglobulin is a useful marker of prognosis - raised levels imply poor prognosis. Low levels of albumin are also associated with a poor prognosis

**International prognostic index**

| Stage | Criteria | Median survival (months) |
|---|---|---|
| I | B2 microglobulin < 3.5 mg/l<br>Albumin > 35 g/l | 62 |
| II | Not I or III | 45 |
| III | B2 microglobulin > 5.5 mg/l | 29 |

# NEOPLASTIC SPINAL CORD COMPRESSION

Spinal cord compression is an oncological emergency and affects up to 5% of cancer patients. Extradural compression accounts for the majority of cases, usually due to vertebral body metastases. It is more common in patients with lung, breast and prostate cancer

Features
- back pain
    - the earliest and most common symptom
    - may be worse on lying down and coughing
- lower limb weakness
- sensory changes: sensory loss and numbness
- neurological signs depend on the level of the lesion. Lesions above L1 usually result in upper motor neuron signs in the legs and a sensory level. Lesions below L1 usually cause lower motor neuron signs in the legs and perianal numbness. Tendon reflexes tend to be increased below the level of the lesion and absent at the level of the lesion

Investigation
- urgent MRI: the 2019 NICE guidelines recommend a whole MRI spine within 24 hours of presentation

Management
- high-dose oral dexamethasone
- urgent oncological assessment for consideration of radiotherapy or surgery

# MYELOFIBROSIS

Overview
- a myeloproliferative disorder
- thought to be caused by hyperplasia of abnormal megakaryocytes
- the resultant release of platelet derived growth factor is thought to stimulate fibroblasts
- haematopoiesis develops in the liver and spleen

Features
- e.g. elderly person with symptoms of anaemia e.g. fatigue (the most common presenting symptom)
- massive splenomegaly
- hypermetabolic symptoms: weight loss, night sweats etc

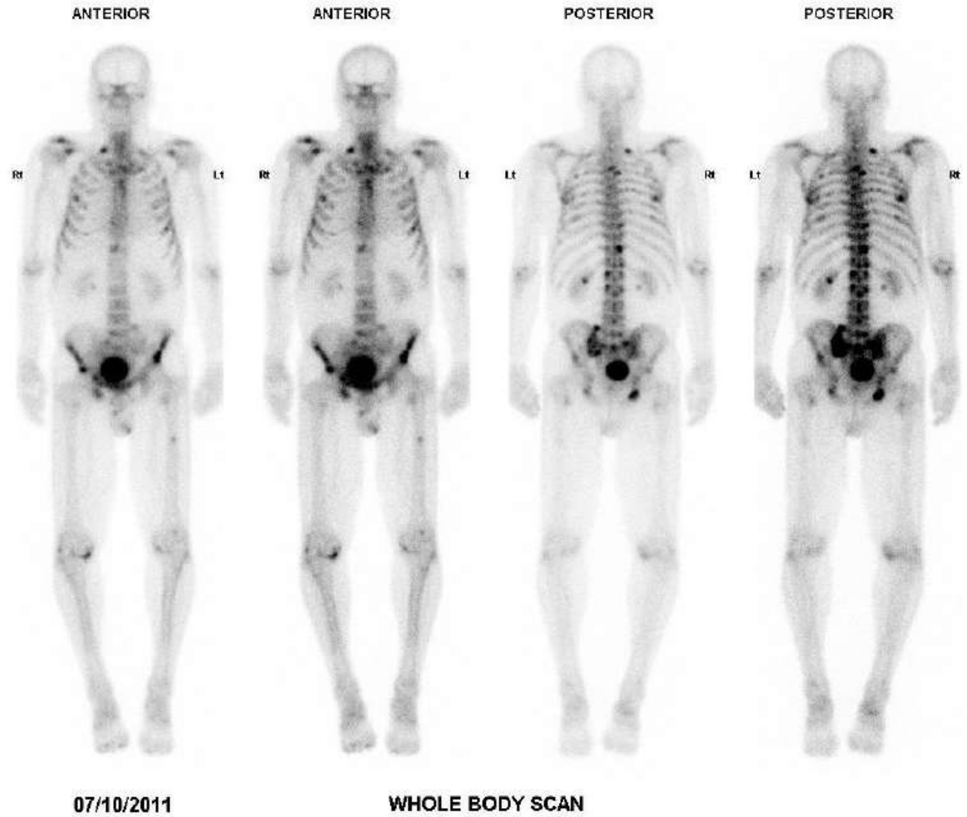
Laboratory findings
- anaemia
- high WBC and platelet count early in the disease
- 'tear-drop' poikilocytes on blood film
- unobtainable bone marrow biopsy - 'dry tap' therefore trephine biopsy needed
- high urate and LDH (reflect increased cell turnover)

# BONE METASTASES

Most common tumour causing bone metastases (in descending order)
- prostate
- breast
- lung

Most common site (in descending order)
- spine
- pelvis
- ribs
- skull
- long bones

Other than bone pain, features may include:
- pathological fractures
- hypercalcaemia
- raised ALP



Isotope bone scan (using technetium-99m labelled diphosphonates which accumulate in the bones) from a patient with metastatic prostate cancer. The scan demonstrates multiple, irregular, randomly distributed foci of high grade activity involving the spine, ribs, sternum, pelvic and femoral bones. The findings are in keeping with multiple osteoblastic metastasis.

## SPINAL METASTASES

Patients may present with spinal metastases before developing metastatic spinal cord compression. It is, therefore, important to detect these patients early before any neurological compromise develops.

Symptoms and findings

- Unrelenting lumbar back pain
- Any thoracic or cervical back pain
- Worse with sneezing, coughing or straining
- Nocturnal
- Associated with tenderness

If any neurological features are present then spinal cord compression must be suspected and acted on promptly. Without neurological features, a whole spine MRI should be completed within one week. The whole spine should be imaged as patients commonly present with multi-level disease.

Sources:

Al-Qurainy, Rasha, and Emily Collis. 'Metastatic Spinal Cord Compression: Diagnosis and Management.' Bmj (2016): I2539.

Metastatic Spinal Cord Compression in Adults: Risk Assessment, Diagnosis and Management Clinical Guideline [CG75]. National Institute of Clinical Excellence. N.p., Nov. 2008.

# THYMOMA

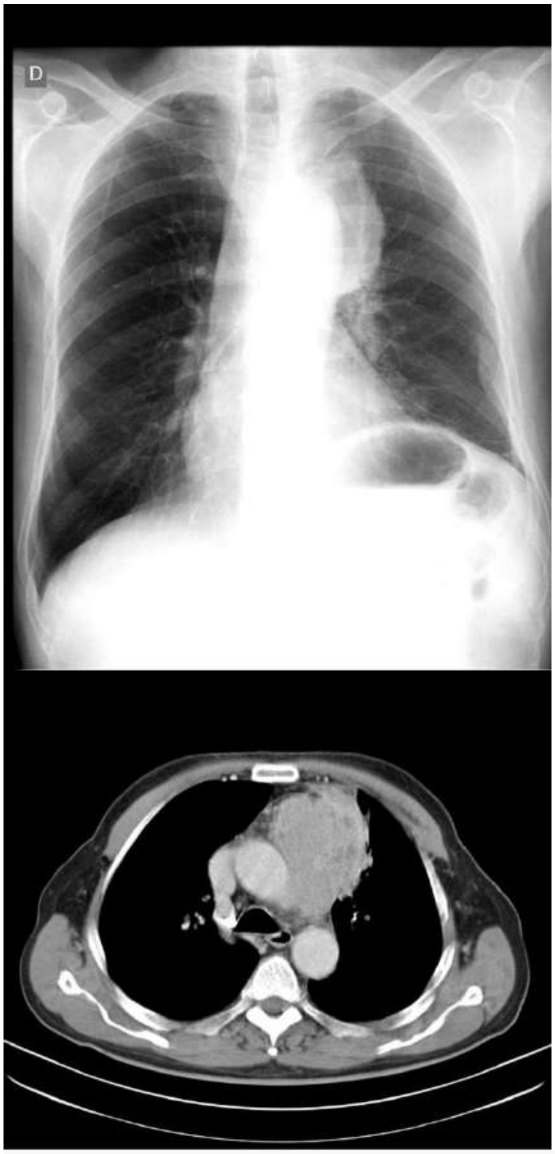
Thymomas are the most common tumour of the anterior mediastinum and is usually detected between the sixth and seventh decades of life.

Associated with

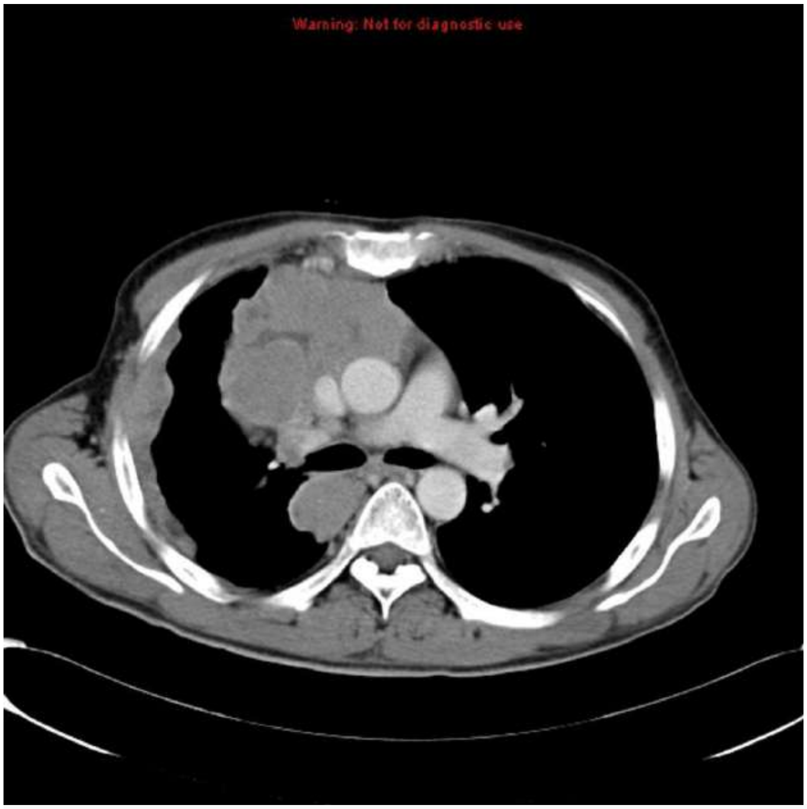
- myasthenia gravis (30-40% of patients with thymoma)
- red cell aplasia
- dermatomyositis
- also : SLE, SIADH

Causes of death

- compression of airway
- cardiac tamponade



Chest x-ray and accompanying CT scan of a patient with a thymoma. In the chest x-ray there is a partially delineated mediastinal mass (anterior mediastinum) with regular borders, bulging the left upper mediastinal contour.


Warning: Not for diagnostic use

CT slice at the bifurcation of the main bronchus showing an invasive thymoma presenting as an anterior mediastinal mass

# ECOG SCORE

The ECOG score is a 'performance status' scale, or a score that measures the functional status a patient. It is used to decide if a patient is a good or poor candidate for future oncological therapies. Those with a poor functional status is a poor candidate for further chemotherapy.

| | |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled; cannot carry on any selfcare; totally confined to bed or chair |
| 5 | Dead |

# CYTOTOXIC AGENTS

The tables below summarises the mechanism of action and major adverse effects of commonly used cytotoxic agents.

### Alkylating agents

| Cytotoxic | Mechanism of action | Adverse effects |
|---|---|---|
| Cyclophosphamide | Alkylating agent - causes cross-linking in DNA | Haemorrhagic cystitis, myelosuppression, transitional cell carcinoma |

### Cytotoxic agents

| Cytotoxic | Mechanism of action | Adverse effects |
|---|---|---|
| Bleomycin | Degrades preformed DNA | Lung fibrosis |
| Anthracyclines (e.g doxorubicin) | Stabilizes DNA-topoisomerase II complex inhibits DNA & RNA synthesis | Cardiomyopathy |

### Antimetabolites

| Cytotoxic | Mechanism of action | Adverse effects |
|---|---|---|
| Methotrexate | Inhibits dihydrofolate reductase and thymidylate synthesis | Myelosuppression, mucositis, liver fibrosis, lung fibrosis |
| Fluorouracil (5-FU) | Pyrimidine analogue inducing cell cycle arrest and apoptosis by blocking | Myelosuppression, mucositis, dermatitis |

| Cytotoxic | Mechanism of action | Adverse effects |
|---|---|---|
| | thymidylate synthase (works during S phase) | |
| 6-mercaptopurine | Purine analogue that is activated by HGPRTase, decreasing purine synthesis | Myelosuppression |
| Cytarabine | Pyrimidine antagonist. Interferes with DNA synthesis specifically at the S-phase of the cell cycle and inhibits DNA polymerase | Myelosuppression, ataxia |

**Acts on microtubules**

| Cytotoxic | Mechanism of action | Adverse effects |
|---|---|---|
| Vincristine, vinblastine | Inhibits formation of microtubules | Vincristine: Peripheral neuropathy (reversible) , paralytic ileus<br>Vinblastine: myelosuppression |
| Docetaxel | Prevents microtubule depolymerisation & disassembly, decreasing free tubulin | Neutropaenia |

**Topoisomerase Inhibitors**

| Cytotoxic | Mechanism of action | Adverse effects |
|---|---|---|
| Irinotecan | Inhibits topoisomerase I which prevents relaxation of supercoiled DNA | Myelosuppression |

**Other cytotoxic drugs**

| Cytotoxic | Mechanism of action | Adverse effects |
|---|---|---|
| Cisplatin | Causes cross-linking in DNA | Ototoxicity, peripheral neuropathy, hypomagnesaemia |
| Hydroxyurea (hydroxycarbamide) | Inhibits ribonucleotide reductase, decreasing DNA synthesis | Myelosuppression |

# CHEMOTHERAPY SIDE-EFFECTS: NAUSEA AND VOMITING

Nausea and vomiting are common side-effects of chemotherapy. Risk factors for the development of symptoms include:

- anxiety
- age less than 50 years old
- concurrent use of opioids
- the type of chemotherapy used

For patients at low-risk of symptoms then drugs such as metoclopramide may be used first-line. For high-risk patients then 5HT3 receptor antagonists such as ondansetron are often effective, especially if combined with dexamethasone

# SUPERIOR VENA CAVA OBSTRUCTION

Superior vena cava (SVC) obstruction is an oncological emergency caused by compression of the SVC. It is most commonly associated with lung cancer.

Features
- dyspnoea is the most common symptom
- swelling of the face, neck and arms - conjunctival and periorbital oedema may be seen
- headache: often worse in the mornings
- visual disturbance
- pulseless jugular venous distension

Causes
- common malignancies: small cell lung cancer, lymphoma
- other malignancies: metastatic seminoma, Kaposi's sarcoma, breast cancer
- aortic aneurysm
- mediastinal fibrosis
- goitre
- SVC thrombosis

Management
- general: dexamethasone, balloon venoplasty, stenting
- small cell: chemotherapy + radiotherapy
- non-small cell: radiotherapy

# HEREDITARY ANGIOEDEMA

Hereditary angioedema is an autosomal dominant condition associated with low plasma levels of the C1 inhibitor (C1-INH) protein. C1-INH is a multifunctional serine protease inhibitor - the probable mechanism behind attacks is uncontrolled release of bradykinin resulting in oedema of tissues.

Investigation
- C1-INH level is low during an attack
- low C2 and C4 levels are seen, even between attacks. Serum C4 is the most reliable and widely used screening tool

Symptoms
- attacks may be proceeded by painful macular rash
- painless, non-pruritic swelling of subcutaneous/submucosal tissues
- may affect upper airways, skin or abdominal organs (can occasionally present as abdominal pain due to visceral oedema)

- urticaria is not usually a feature

Management
- acute: IV C1-inhibitor concentrate, fresh frozen plasma (FFP) if this is not available
- prophylaxis: anabolic steroid Danazol may help

# BLOOD PRODUCTS: FFP, CRYOPRECIPITATE AND PROTHROMBIN COMPLEX

NICE published guidelines on the use of blood products in 2015.

Fresh frozen plasma (FFP)

- most suited for 'clinically significant' but without 'major haemorrhage' in patients with a prothrombin time (PT) ratio or activated partial thromboplastin time (APTT) ratio > 1.5
- typically 150-220 mL
- can be used prophylactically in patients undergoing invasive surgery where there is a risk of significant bleeding
- In contrast to red cells, the universal donor of FFP is AB blood because it lacks any anti-A or anti-B antibodies

Cryoprecipitate

- contains concentrated Factor VIII:C, von Willebrand factor, fibrinogen, Factor XIII and fibronectin, produced by further processing of Fresh Frozen Plasma (FFP). Clinically it is most commonly used to replace fibrinogen
- much smaller volume than FFP, typically 15-20mL
- most suited for patients for 'clinically significant' but without 'major haemorrhage' who have a fibrinogen concentration < 1.5 g/L
- example use cases include disseminated intravascular coagulation, liver failure and hypofibrinogenaemia secondary to massive transfusion. It may also be used in an emergency situation for haemophiliacs (when specific factors not available) and in von Willebrand disease
- can be used prophylactically in patients undergoing invasive surgery where there is a risk of significant bleeding where the fibrinogen concentration < 1.0 g/L

Prothrombin complex concentrate

- used for the emergency reversal of anticoagulation in patients with either severe bleeding or a head injury with suspected intracerebral haemorrhage
- can be used prophylactically in patients undergoing emergency surgery depending on the particular circumstance

# BLOOD PRODUCTS: CMV NEGATIVE AND IRRADIATED BLOOD

Cytomegalovirus (CMV) is transmitted in leucocytes. As most blood products (except granulocyte transfusions) are now leucocyte depleted CMV negative products are rarely required.

Irradiated blood products are used to avoid transfusion graft versus host disease (TA-GVHD) caused by engraftment of viable donor T lymphocytes.

The table below shows the indications for CMV and irradiated blood:

| Situation | CMV negative | Irradiated |
|---|---|---|
| Granulocyte transfusions | ✓ | ✓ |
| Intra-uterine transfusions | ✓ | ✓ |
| Neonates up to 28 days post expected date of delivery | ✓ | ✓ |
| Pregnancy: Elective transfusions during pregnancy (not during labour or delivery) | ✓ | |
| Bone marrow / stem cell transplants | | ✓ |
| Immunocompromised (e.g. chemotherapy or congenital) | | ✓ |
| Patients with/previous Hodgkins Disease | | ✓ |
| HIV | | |

# PLATELET TRANSFUSION: ACTIVE BLEEDING

**Active bleeding**
Offer platelet transfusions to patients with a platelet count of <30 x 10 9 with clinically significant bleeding (World Health organisation bleeding grade 2- e.g. haematemesis, melaena, prolonged epistaxis)

Platelet thresholds for transfusion are higher (maximum < 100 x 10 9) for patients with severe bleeding (World Health organisation bleeding grades 3&4), or bleeding at critical sites, such as the CNS.

It should be noted that platelet transfusions have the highest risk of bacterial contamination compared to other types of blood product.

**Pre-invasive procedure (prophylactic)**
Platelet transfusion for thrombocytopenia before surgery/ an invasive procedure. Aim for plt levels of:

- > 50×109/L for most patients
- > 50-75×109/L if high risk of bleeding
- > 100×109/L if surgery at critical site

**If no active bleeding or planned invasive procedure**
A threshold of 10 x 109 except where platelet transfusion is contradindicated or there are alternative treatments for their condition

For example, do not perform platelet transfusion for any of the following conditions:

- Chronic bone marrow failure
- Autoimmune thrombocytopenia
- Heparin-induced thrombocytopenia, or

- Thrombotic thrombocytopenic purpura.

# BLOOD PRODUCT TRANSFUSION COMPLICATIONS

Blood product transfusion complications may be broadly classified into the following:

- immunological: acute haemolytic, non-haemolytic febrile, allergic/anaphylaxis
- infective
- transfusion-related acute lung injury (TRALI)
- transfusion-associated circulatory overload (TACO)
- other: hyperkalaemia, iron overload, clotting

The table below summaries some of the key features:

| Reaction | Features | Management |
|---|---|---|
| **Non-haemolytic febrile reaction**<br>Thought to be caused by antibodies reacting with white cell fragments in the blood product and cytokines that have leaked from the blood cell during storage | Fever, chills<br>Red cell transfusion (1-2%)<br>Platelet transfusion (10-30%) | Slow or stop the transfusion<br>Paracetamol<br>Monitor |
| **Minor allergic reaction**<br>Thought to be caused by foreign plasma proteins | Pruritus, urticaria | Temporarily stop the transfusion<br>Antihistamine<br>Monitor |
| **Anaphylaxis**<br>Can be caused by patients with IgA deficiency who have anti-IgA antibodies | Hypotension, dyspnoea, wheezing, angioedema. | Stop the transfusion<br>IM adrenaline<br>ABC support<br>• oxygen<br>• fluids |
| **Acute haemolytic reaction**<br>ABO-incompatible blood e.g. secondary to human error | Fever, abdominal pain, hypotension | Stop transfusion<br>Confirm diagnosis<br>• check the identity of patient/name on blood product |

| Reaction | Features | Management |
|---|---|---|
| | | - send blood for direct Coombs test, repeat typing and cross-matching<br>Supportive care<br>- fluid resuscitation |
| **Transfusion-associated circulatory overload (TACO)**<br>Excessive rate of transfusion, pre-existing heart failure | Pulmonary oedema, hypertension | Slow or stop transfusion<br>Consider intravenous loop diuretic (e.g. furosemide) and oxygen |
| **Transfusion-related acute lung injury (TRALI)**<br>Non-cardiogenic pulmonary oedema thought to be secondary to increased vascular permeability caused by host neutrophils that become activated by substances in donated blood | Hypoxia, pulmonary infiltrates on chest x-ray, fever, hypotension | Stop the transfusion<br>Oxygen and supportive care |

Further information is provided below:

**Acute haemolytic transfusion reaction**
Acute haemolytic transfusion reaction results from a mismatch of blood group (ABO) which causes massive intravascular haemolysis. This is usually the result of red blood cell destruction by IgM-type antibodies.

Symptoms begin minutes after the transfusion is started and include a fever, abdominal and chest pain, agitation and hypotension.

Treatment should include immediate transfusion termination, generous fluid resuscitation with saline solution and informing the lab

Complications include disseminated intravascular coagulation, and renal failure

**Non-haemolytic febrile reaction**
Febrile reactions

- due to white blood cell HLA antibodies
- often the result of sensitization by previous pregnancies or transfusions
- paracetamol may be given

**Allergic/anaphylaxis reaction**

Allergic reactions to blood transfusions are caused by hypersensitivity reactions to components within the transfusion. Symptoms typically arise within minutes of starting the transfusion and severity can range from urticaria to anaphylaxis with hypotension, dyspnoea, wheezing, and stridor, or angioedema.

Simple urticaria should be treated by discontinuing the transfusion and with an antihistamine. Once the symptoms resolve, the transfusion may be continued with no need for further workup.

More severe allergic reaction or anaphylaxis should be treated urgently. The transfusion should be permanently discontinued, intramuscular adrenaline should be administered and supportive care. Antihistamine, corticosteroids and bronchodilators should also be considered for these patients.

**Transfusion-related acute lung injury (TRALI)**

A rare but potentially fatal complication of blood transfusion. Characterised by the development of hypoxaemia / acute respiratory distress syndrome within 6 hours of transfusion. Features include:

- hypoxia
- pulmonary infiltrates on chest x-ray
- fever
- hypotension

**Transfusion-associated circulatory overload (TACO)**

A relatively common reaction due to fluid overload resulting in pulmonary oedema. As well as features of pulmonary oedema the patient may also by hypertensive, a key difference from patients with TRALI.

**Infective**

Transmission of vCJD

- although the absolute risk is very small, vCJD may be transmitted via blood transfusion
- a number of steps have been taken to minimise this risk, including:
  - from late 1999 onward, all donations have undergone removal of white cells (leucodepletion) in order to reduce any vCJD infectivity present
  - from 1999, plasma derivatives have been fractionated from imported plasma rather than being sourced from UK donors. Fresh Frozen Plasma (FFP) used for children and certain groups of adults needing frequent transfusions is also imported
  - from 2004 onward, recipients of blood components have been excluded from donating blood

# TRANEXAMIC ACID

Tranexamic acid is a synthetic derivative of lysine. Its primary mode of action is as an antifibrinolytic that reversibly binds to lysine receptor sites on plasminogen or plasmin. This prevents plasmin from binding to and degrading fibrin.

Tranexamic acid is most commonly prescribed to help treat menorrhagia.

The role of tranexamic acid in trauma was investigated in the CRASH 2 trial and has been shown to be of benefit in bleeding trauma when administered in the first 3 hours. Tranexamic acid is given as an IV bolus followed by an infusion in cases of major haemorrhage.

There is also ongoing research looking at the role of tranexamic acid in traumatic brain injury.

# ALLERGY TESTS

| | |
|---|---|
| **Skin prick test** | **Most commonly used test as easy to perform and inexpensive. Drops of diluted allergen are placed on the skin after which the skin is pierced using a needle. A large number of allergens can be tested in one session. Normally includes a histamine (positive) and sterile water (negative) control. A wheal will typically develop if a patient has an allergy. Can be interpreted after 15 minutes**<br>**Useful for food allergies and also pollen** |
| Radioallergosorbent test (RAST) | Determines the amount of IgE that reacts specifically with suspected or known allergens, for example IgE to egg protein. Results are given in grades from 0 (negative) to 6 (strongly positive)<br>Useful for food allergies, inhaled allergens (e.g. Pollen) and wasp/bee venom<br>Blood tests may be used when skin prick tests are not suitable, for example if there is extensive eczema or if the patient is taking antihistamines |
| Skin patch testing | Useful for contact dermatitis. Around 30-40 allergens are placed on the back. Irritants may also be tested for. The patches are removed 48 hours later with the results being read by a dermatologist after a further 48 hours |

# LATEX ALLERGY

Sensitivity to latex may cause a number of problems:
- type I hypersensitivity (anaphylaxis)
- type IV hypersensitivity (allergic contact dermatitis)
- irritant contact dermatitis

Latex allergy is more common in children with myelomeningocele spina bifida.

**Latex-fruit syndrome**
It is recognised that many people who are allergic to latex are also allergic to fruits, particularly banana, pineapple, avocado, chestnut, kiwi fruit, mango, passion fruit and strawberry.

# ANAPHYLAXIS

Anaphylaxis may be defined as a severe, life-threatening, generalised or systemic hypersensitivity reaction.

Common identified causes of anaphylaxis:

- food (e.g. nuts) - the most common cause in children
- drugs
- venom (e.g. wasp sting)

Anaphylaxis is one of the few times when you would not have time to look up the dose of a medication. The Resuscitation Council guidelines on anaphylaxis have recently been updated. Adrenaline is by far the most important drug in anaphylaxis and should be given as soon as possible. The recommended doses for adrenaline, hydrocortisone and chlorphenamine are as follows:

| | **Adrenaline** | **Hydrocortisone** | **Chlorphenamine** |
|---|---|---|---|
| **< 6 months** | 150 micrograms (0.15ml 1 in 1,000) | 25 mg | 250 micrograms/kg |
| **6 months - 6 years** | 150 micrograms (0.15ml 1 in 1,000) | 50 mg | 2.5 mg |
| **6-12 years** | 300 micrograms (0.3ml 1 in 1,000) | 100 mg | 5 mg |
| **Adult and child > 12 years** | 500 micrograms (0.5ml 1 in 1,000) | 200 mg | 10 mg |

Adrenaline can be repeated every 5 minutes if necessary. The best site for IM injection is the anterolateral aspect of the middle third of the thigh.

Management following stabilisation:

- patients who have had emergency treatment for anaphylaxis should be observed for 6–12 hours from the onset of symptoms, as it is known that biphasic reactions can occur in up to 20% of patients
- sometimes it can be difficult to establish whether a patient had a true episode of anaphylaxis. Serum tryptase levels are sometimes taken in such patients as they remain elevated for up to 12 hours following an acute episode of anaphylaxis.

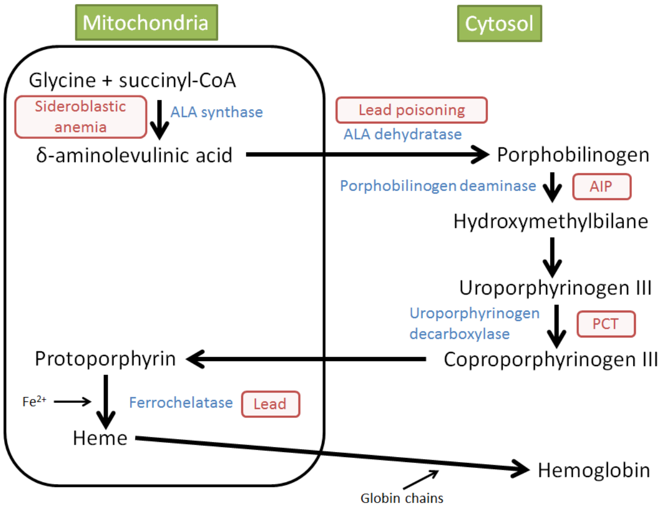
# LEAD POISONING

Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of abdominal pain and neurological signs. Lead poisoning results in defective ferrochelatase and ALA dehydratase function.

Features
- abdominal pain
- peripheral neuropathy (mainly motor)
- fatigue
- constipation
- blue lines on gum margin (only 20% of adult patients, very rare in children)

Investigations
- the blood lead level is usually used for diagnosis. Levels greater than 10 mcg/dl are considered significant
- full blood count: microcytic anaemia. Blood film shows red cell abnormalities including basophilic stippling and clover-leaf morphology
- raised serum and urine levels of delta aminolaevulinic acid may be seen making it sometimes difficult to differentiate from acute intermittent porphyria
- urinary coproporphyrin is also increased (urinary porphobilinogen and uroporphyrin levels are normal to slightly increased)
- in children, lead can accumulate in the metaphysis of the bones although x-rays are not part of the standard work-up

Management - various chelating agents are currently used:
- dimercaptosuccinic acid (DMSA)
- D-penicillamine
- EDTA
- dimercaprol


Mitochondria
Cytosol
Glycine + succinyl-CoA
Sideroblastic anemia
ALA synthase
δ-aminolevulinic acid
Lead poisoning
ALA dehydratase
Porphobilinogen
Porphobilinogen deaminase
AIP
Hydroxymethylbilane
Uroporphyrinogen III
Uroporphyrinogen decarboxylase
PCT
Coproporphyrinogen III
Protoporphyrin
Fe2+
Ferrochelatase
Lead
Heme
Hemoglobin
Globin chains

# LEUCOCYTE ALKALINE PHOSPHATASE

Raised in
- myelofibrosis
- leukaemoid reactions
- polycythaemia rubra vera
- infections
- steroids, Cushing's syndrome
- pregnancy, oral contraceptive pill

Low in
- chronic myeloid leukaemia
- pernicious anaemia
- paroxysmal nocturnal haemoglobinuria
- infectious mononucleosis

# POSITRON EMISSION TOMOGRAPHY (PET)

Positron Emission Tomography (PET) is a form of nuclear imaging which uses fluorodeoxyglucose (FDG) as the radiotracer. This allows a 3D image of metabolic activity to be generated using glucose uptake as a proxy marker. The images obtained are then combined with a conventional imaging technique such as CT to decide whether lesions are metabolically active.

Uses
- evaluating primary and possible metastatic disease
- cardiac PET: not used mainstream currently

# PASSMEDICINE NOTES ENDOCRINOLOGY

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# DIABETES: PATHOPHYSIOLOGY

Type 1 DM

- autoimmune disease
- antibodies against beta cells of pancreas
- HLA DR4 > HLA DR3
- various antibodies such as islet-associated antigen (IAA) antibody and glutamic acid decarboxylase (GAD) antibody are detected in patients who later go on to develop type 1 DM - their prognostic significance is not yet clear

# DIABETES MELLITUS: A VERY BASIC INTRODUCTION

Diabetes mellitus is one of the most common conditions encountered in clinical practice and represents a significant burden on the health systems of the developed world. It is now estimated that 8% of the total NHS budget is now spent on managing patients with diabetes mellitus.

**What is diabetes mellitus?**
Diabetes mellitus may be defined as a chronic condition characterised by abnormally raised levels of blood glucose.

**Why is the management of diabetes mellitus so important?**
Before the advent of insulin therapy untreated type 1 diabetes would usually result in death. Poorly treated type 1 diabetes mellitus can still result in significant morbidity and mortality (as a result of diabetic ketoacidosis). However, the main focus of diabetes management now is reducing the incidence of macrovascular (ischaemic heart disease, stroke) and microvascular (eye, nerve and kidney damage) complications.

| Type | Notes |
|---|---|
| **Type 1 diabetes mellitus (T1DM)** | Autoimmune disorder where the insulin-producing beta cells of the islets of Langerhans in the pancreas are destroyed by the immune system<br>This results in an absolute deficiency of insulin resulting in raised glucose levels<br>Patients tend to develop T1DM in childhood/early adult life and typically present unwell, possibly in diabetic ketoacidosis |
| **Type 2 diabetes mellitus (T2DM)** | This is the most common cause of diabetes in the developed world. It is caused by a relative deficiency of insulin due to an excess of adipose tissue. In simple terms there isn't enough insulin to 'go around' all the excess fatty tissue, leading to blood glucose creeping up. |
| **Prediabetes** | This term is used for patients who don't yet meet the criteria for a formal diagnosis of T2DM to be made but are likely to develop the condition over the next few years. They, therefore, require closer monitoring and lifestyle interventions such as weight loss |
| **Gestational diabetes** | Some pregnant develop raised glucose levels during pregnancy. This is important to detect as untreated it may lead to adverse outcomes for the mother and baby |

| Type | Notes |
|---|---|
| **Maturity onset diabetes of the young (MODY)** | A group of inherited genetic disorders affecting the production of insulin. Results in younger patients developing symptoms similar to those with T2DM, i.e. asymptomatic hyperglycaemia with progression to more severe complications such as diabetic ketoacidosis |
| **Latent autoimmune diabetes of adults (LADA)** | The majority of patients with autoimmune-related diabetes present younger in life. There are however a small group of patients who develop such problems later in life. These patients are often misdiagnosed as having T2DM |
| **Other types** | Any pathological process which damages the insulin-producing cells of the pancreas may cause diabetes to develop. Examples include chronic pancreatitis and haemochromatosis.<br>Drugs may also cause raised glucose levels. A common example is glucocorticoids which commonly result in raised blood glucose levels |

**Symptoms and signs**

The presentation of diabetes mellitus depends very much on the type:

| Type 1 DM | Type 2 DM |
|---|---|
| Weight loss<br>Polydipsia<br>Polyuria<br>May present with diabetic ketoacidosis<br>• abdominal pain<br>• vomiting<br>• reduced consciousness level | Often picked up incidentally on routine blood tests<br>Polydipsia<br>Polyuria |

Remember that the polyuria and polydipsia are due to water being 'dragged' out of the body due to the osmotic effects of excess blood glucose being excreted in the urine (glycosuria).

**Investigations**

There are 4 main ways to check blood glucose:

- a finger-prick bedside glucose monitor
- a one-off blood glucose. This may either be fasting or non-fasting
- a HbA1c. This measures the amount of glycosylated haemoglobin and represents the average blood glucose over the past 2-3 months
- a glucose tolerance test. In this test, a fasting blood glucose is taken after which a 75g glucose load is taken. After 2 hours a second blood glucose reading is then taken

The diagnostic criteria are determined by WHO.

If the patient is symptomatic:

- fasting glucose greater than or equal to 7.0 mmol/l
- random glucose greater than or equal to 11.1 mmol/l (or after 75g oral glucose tolerance test)

If the patient is asymptomatic the above criteria apply but must be demonstrated on two separate occasions.

In 2011 WHO released supplementary guidance on the use of HbA1c for the diagnosis of diabetes:

- a HbA1c of greater than or equal to 6.5% (48 mmol/mol) is diagnostic of diabetes mellitus
- a HbAlc value of less than 6.5% does not exclude diabetes (i.e. it is not as sensitive as fasting samples for detecting diabetes)
- in patients without symptoms, the test must be repeated to confirm the diagnosis
- it should be remembered that misleading HbA1c results can be caused by increased red cell turnover

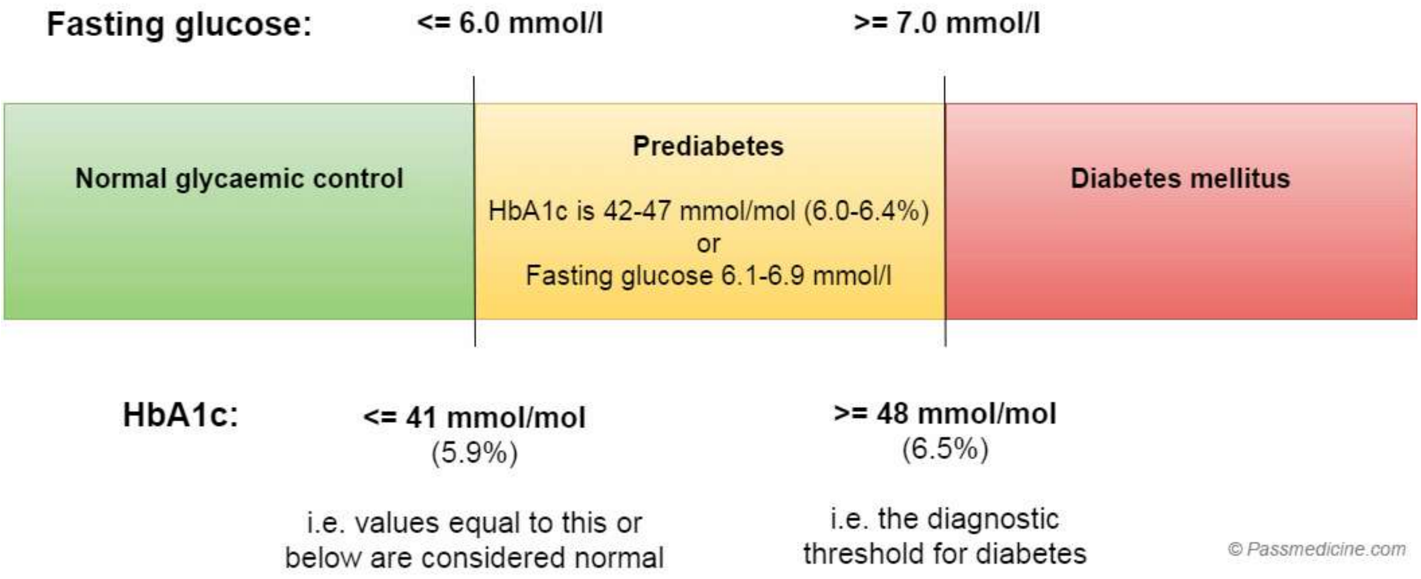
Fasting glucose:
<= 6.0 mmol/l
>= 7.0 mmol/l
Normal glycaemic control
Prediabetes
HbA1c is 42-47 mmol/mol (6.0-6.4%)
or
Fasting glucose 6.1-6.9 mmol/l
Diabetes mellitus
HbA1c:
<= 41 mmol/mol
(5.9%)
i.e. values equal to this or below are considered normal
>= 48 mmol/mol
(6.5%)
i.e. the diagnostic threshold for diabetes
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Diagram showing the spectrum of diabetes diagnosis

**Management**

The principle of managing diabetes mellitus are as follows:

- drug therapy to normalise blood glucose levels
- monitoring for and treating any complications related to diabetes
- modifying any other risk factors for other conditions such as cardiovascular disease

Type 1 diabetes

- patients always require insulin to control the blood sugar levels. This is because there is an absolute deficiency of insulin with no pancreatic tissue left to stimulate with drugs
- different types of insulin are available according to their duration of action

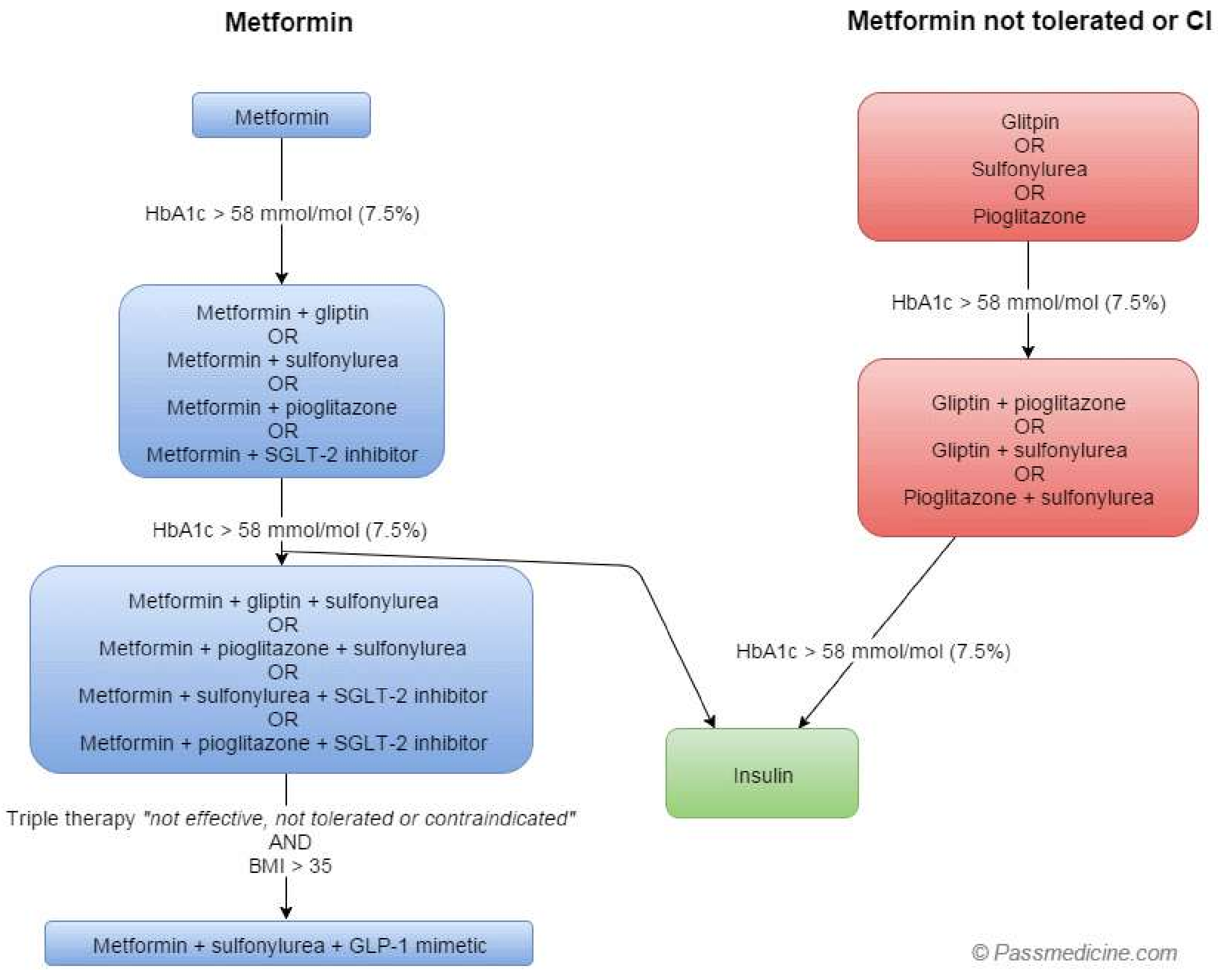
Type 2 diabetes

- the majority of patients with type 2 diabetes are controlled using oral medication
- the first-line drug for the vast majority of patients is metformin
- second-line drugs include sulfonylureas, gliptins and pioglitazone. Please see the table below for further information
- if oral medication is not controlling the blood glucose to a sufficient degree then insulin is used

The table below shows some of the main drugs used in the management of diabetes mellitus:

| Drug class | Mechanism of action | Route | Main side-effects | Notes |
|---|---|---|---|---|
| **Insulin** | Direct replacement for endogenous insulin | Subcutaneous | Hypoglycaemia<br>Weight gain<br>Lipodystrophy | Used in all patients with T1DM and some patients with poorly controlled T2DM<br><br>Can be classified according to source (analogue, human sequence and porcine) and duration of action (short, immediate, long-acting) |
| **Metformin** | Increases insulin sensitivity<br>Decreases hepatic gluconeogenesis | Oral | Gastrointestinal upset<br>Lactic acidosis* | First-line medication in the management of T2DM<br><br>Cannot be used in patients with an eGFR of < 30 ml/min |
| **Sulfonylureas** | Stimulate pancreatic beta cells to secrete insulin | Oral | Hypoglycaemia<br>Weight gain<br>Hyponatraemia | Examples include gliclazide and glimepiride |
| **Thiazolidinediones** | Activate PPAR-gamma receptor in adipocytes to promote adipogenesis and fatty acid uptake | Oral | Weight gain<br>Fluid retention | Only currently available thiazolidinedione is pioglitazone |
| **DPP-4 inhibitors (-gliptins)** | Increases incretin levels which inhibit glucagon secretion | Oral | Generally well tolerated but increased risk of pancreatitis | |
| **SGLT-2 inhibitors (-gliflozins)** | Inhibits reabsorption of glucose in the kidney | Oral | Urinary tract infection | Typically result in weight loss |
| **GLP-1 agonists** (-tides) | Incretin mimetic which inhibits glucagon secretion | Subcutaneous | Nausea and vomiting<br>Pancreatitis | Typically result in weight loss |

NICE provide guidelines on how drug therapy should be used in T2DM:


Metformin
Metformin not tolerated or CI
Metformin
HbA1c > 58 mmol/mol (7.5%)
Metformin + gliptin OR Metformin + sulfonylurea OR Metformin + pioglitazone OR Metformin + SGLT-2 inhibitor
HbA1c > 58 mmol/mol (7.5%)
Metformin + gliptin + sulfonylurea OR Metformin + pioglitazone + sulfonylurea OR Metformin + sulfonylurea + SGLT-2 inhibitor OR Metformin + pioglitazone + SGLT-2 inhibitor
Triple therapy "not effective, not tolerated or contraindicated" AND BMI > 35
Metformin + sulfonylurea + GLP-1 mimetic
Glitpin OR Sulfonylurea OR Pioglitazone
HbA1c > 58 mmol/mol (7.5%)
Gliptin + pioglitazone OR Gliptin + sulfonylurea OR Pioglitazone + sulfonylurea
HbA1c > 58 mmol/mol (7.5%)
Insulin
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*common in exams, much less common in clinical practice

# GLYCOSYLATED HAEMOGLOBIN

Glycosylated haemoglobin (HbA1c) is the most widely used measure of long-term glycaemic control in diabetes mellitus. HbA1c is produced by the glycosylation of haemoglobin at a rate proportional to the glucose concentration. The level of HbA1c therefore is dependant on

- red blood cell lifespan
- average blood glucose concentration

A number of conditions can interfere with accurate HbA1c interpretation:

| Lower-than-expected levels of HbA1c (due to reduced red blood cell lifespan) | Higher-than-expected levels of HbA1c (due to increased red blood cell lifespan) |
|---|---|
| Sickle-cell anaemia<br>GP6D deficiency<br>Hereditary spherocytosis | Vitamin B12/folic acid deficiency<br>Iron-deficiency anaemia<br>Splenectomy |

HbA1c is generally thought to reflect the blood glucose over the previous '3 months' although there is some evidence it is weighed more strongly to glucose levels of the past 2-4 weeks. NICE recommend 'HbA1c should be checked every 3-6 months until stable, then 6 monthly'.

The relationship between HbA1c and average blood glucose is complex but has been studied by the Diabetes Control and Complications Trial (DCCT). A new internationally standardised method for reporting HbA1c has been developed by the International Federation of Clinical Chemistry (IFCC). This will report HbA1c in mmol per mol of haemoglobin without glucose attached.

| HBA1c (%) | Average plasma glucose (mmol/l) | IFCC-HbA1c (mmol/mol) |
|---|---|---|
| 5 | 5.5 | |
| 6 | 7.5 | 42 |
| 7 | 9.5 | 53 |
| 8 | 11.5 | 64 |
| 9 | 13.5 | 75 |
| 10 | 15.5 | |
| 11 | 17.5 | |
| 12 | 19.5 | |

From the above we can see that average plasma glucose = (2 * HbA1c) - 4.5

# MODY

Maturity-onset diabetes of the young (MODY) is characterised by the development of type 2 diabetes mellitus in patients < 25 years old. It is typically inherited as an autosomal dominant condition. Over six different genetic mutations have so far been identified as leading to MODY.

It is thought that around 1-2% of patients with diabetes mellitus have MODY, and around 90% are misclassified as having either type 1 or type 2 diabetes mellitus.

MODY 3
- 60% of cases
- due to a defect in the HNF-1 alpha gene
- is associated with an increased risk of HCC

MODY 2
- 20% of cases
- due to a defect in the glucokinase gene

MODY 5
- rare
- due to a defect in the HNF-1 beta gene
- liver and renal cysts

Features of MODY

- typically develops in patients < 25 years
- a family history of early onset diabetes is often present
- ketosis is not a feature at presentation
- patients with the most common form are very sensitive to sulfonylureas, insulin is not usually necessary

## DIABETES MELLITUS (TYPE 2): DIAGNOSIS

The diagnosis of type 2 diabetes mellitus can be made by either a plasma glucose or a HbA1c sample. Diagnostic criteria vary according to whether the patient is symptomatic (polyuria, polydipsia etc) or not.

If the patient is symptomatic:

- fasting glucose greater than or equal to 7.0 mmol/l
- random glucose greater than or equal to 11.1 mmol/l (or after 75g oral glucose tolerance test)

If the patient is asymptomatic the above criteria apply but must be demonstrated on two separate occasions.

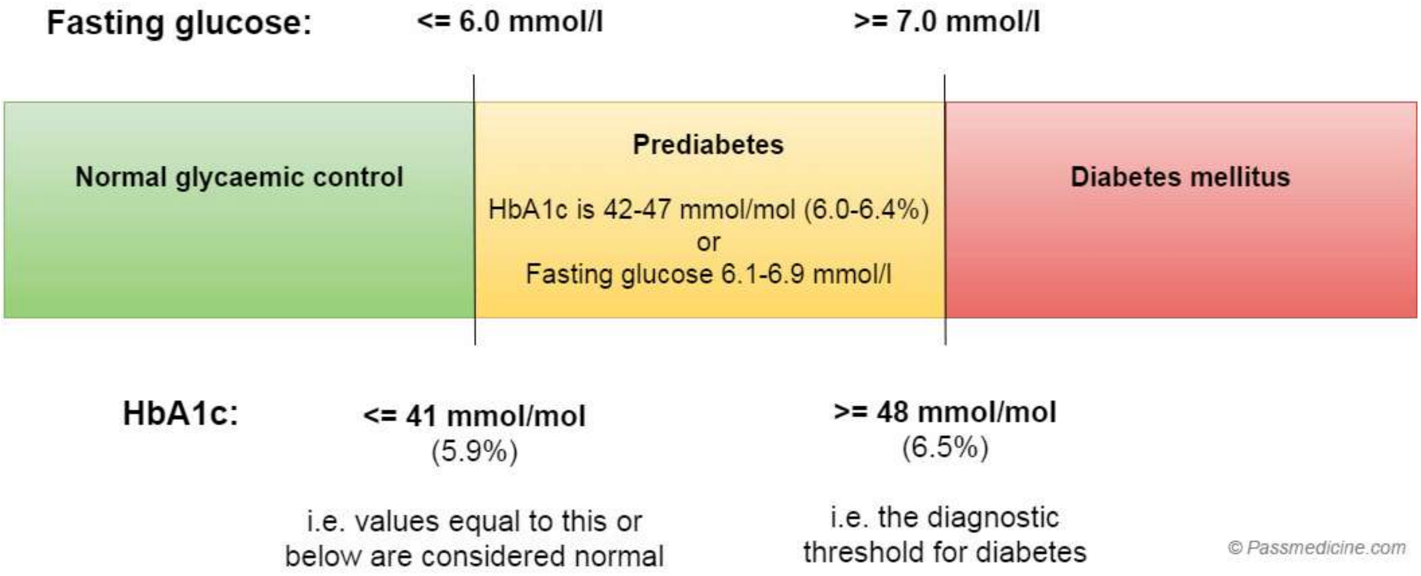
Fasting glucose:
<= 6.0 mmol/l
>= 7.0 mmol/l
Normal glycaemic control
Prediabetes
HbA1c is 42-47 mmol/mol (6.0-6.4%)
or
Fasting glucose 6.1-6.9 mmol/l
Diabetes mellitus
HbA1c:
<= 41 mmol/mol
(5.9%)
i.e. values equal to this or below are considered normal
>= 48 mmol/mol
(6.5%)
i.e. the diagnostic threshold for diabetes
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Diagram showing the spectrum of diabetes diagnosis

In 2011 WHO released supplementary guidance on the use of HbA1c on the diagnosis of diabetes:

- a HbA1c of greater than or equal to 48 mmol/mol (6.5%) is diagnostic of diabetes mellitus
- a HbAlc value of less than 48 mmol/mol (6.5%) does not exclude diabetes (i.e. it is not as sensitive as fasting samples for detecting diabetes)

- in patients without symptoms, the test must be repeated to confirm the diagnosis
- it should be remembered that misleading HbA1c results can be caused by increased red cell turnover (see below)

Conditions where HbA1c may not be used for diagnosis:
- haemoglobinopathies
- haemolytic anaemia
- untreated iron deficiency anaemia
- suspected gestational diabetes
- children
- HIV
- chronic kidney disease
- people taking medication that may cause hyperglycaemia (for example corticosteroids)

**Impaired fasting glucose and impaired glucose tolerance**

A fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l implies impaired fasting glucose (IFG)

Impaired glucose tolerance (IGT) is defined as fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l

Diabetes UK suggests:
- 'People with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT.'

# PREDIABETES AND IMPAIRED GLUCOSE REGULATION

Prediabetes is a term which is increasingly used where there is impaired glucose levels which are above the normal range but not high enough for a diagnosis of diabetes mellitus. The term includes patients who have been labelled as having either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Diabetes UK estimate that around 1 in 7 adults in the UK have prediabetes. Many individuals with prediabetes will progress on to developing type 2 diabetes mellitus (T2DM) and they are therefore at greater risk of microvascular and macrovascular complications.

Terminology
- Diabetes UK currently recommend using the term prediabetes when talking to patients and impaired glucose regulation when talking to other healthcare professionals
- research has shown that the term 'prediabetes' has the most impact and is most easily understood

Identification of patients with prediabetes

- NICE recommend using a validated computer based risk assessment tool for all adults aged 40 and over, people of South Asian and Chinese descent aged 25-39, and adults with conditions that increase the risk of type 2 diabetes
- patients identified at high risk should have a blood sample taken
- a fasting plasma glucose of 6.1-6.9 mmol/l or an HbA1c level of 42-47 mmol/mol (6.0-6.4%) indicates high risk

Management

- lifestyle modification: weight loss, increased exercise, change in diet
- at least yearly follow-up with blood tests is recommended
- NICE recommend metformin for adults at high risk *'whose blood glucose measure (fasting plasma glucose or HbA1c) shows they are still progressing towards type 2 diabetes, despite their participation in an intensive lifestyle-change programme'*

**Impaired fasting glucose and impaired glucose tolerance**

There are two main types of IGR:

- impaired fasting glucose (IFG) - due to hepatic insulin resistance
- impaired glucose tolerance (IGT) - due to muscle insulin resistance
- patients with IGT are more likely to develop T2DM and cardiovascular disease than patients with IFG

Definitions

- a fasting glucose greater than or equal to 6.1 but less than 7.0 mmol/l implies impaired fasting glucose (IFG)
- impaired glucose tolerance (IGT) is defined as fasting plasma glucose less than 7.0 mmol/l and OGTT 2-hour value greater than or equal to 7.8 mmol/l but less than 11.1 mmol/l
- people with IFG should then be offered an oral glucose tolerance test to rule out a diagnosis of diabetes. A result below 11.1 mmol/l but above 7.8 mmol/l indicates that the person doesn't have diabetes but does have IGT

# DIABETES MELLITUS: MANAGEMENT OF TYPE 1

The long-term management of type 1 diabetics is an important and complex process requiring the input of many different clinical specialties and members of the healthcare team. A diagnosis of type 1 diabetes can still reduce the life expectancy of patients by 13 years and the micro and macrovascular complications are well documented.

NICE released guidelines on the diagnosis and management of type 1 diabetes in 2015. We've only highlighted a very select amount of the guidance here which will be useful for any clinician looking after a patient with type 1 diabetes.

HbA1c
- should be monitored every 3-6 months
- adults should have a target of HbA1c level of 48 mmol/mol (6.5%) or lower. NICE do however recommend taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia

Self-monitoring of blood glucose
- recommend testing at least 4 times a day, including before each meal and before bed
- more frequent monitoring is recommended if frequency of hypoglycaemic episodes increases; during periods of illness; before, during and after sport; when planning pregnancy, during pregnancy and while breastfeeding

Blood glucose targets
- 5-7 mmol/l on waking and
- 4-7 mmol/l before meals at other times of the day

Type of insulin
- offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults
- twice-daily insulin detemir is the regime of choice. Once-daily insulin glargine or insulin detemir is an alternative
- offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes

Metformin
- NICE recommend considering adding metformin if the BMI >= 25 kg/m²

# DIABETES MELLITUS: MANAGEMENT OF TYPE 2

NICE updated its guidance on the management of type 2 diabetes mellitus (T2DM) in 2015. Key points are listed below:
- HbA1c targets have changed. They are now dependent on what antidiabetic drugs a patient is receiving and other factors such as frailty
- there is more flexibility in the second stage of treating patients (i.e. after metformin has been started) - you now have a choice of 4 oral antidiabetic agents

It's worthwhile thinking of the average patient who is taking metformin for T2DM, you can titrate up metformin and encourage lifestyle changes to aim for a HbA1c of 48 mmol/mol (6.5%), but should only add a second drug if the HbA1c rises to 58 mmol/mol (7.5%)

Dietary advice
- encourage high fibre, low glycaemic index sources of carbohydrates

- include low-fat dairy products and oily fish
- control the intake of foods containing saturated fats and trans fatty acids
- limited substitution of sucrose-containing foods for other carbohydrates is allowable, but care should be taken to avoid excess energy intake
- discourage use of foods marketed specifically at people with diabetes
- initial target weight loss in an overweight person is 5-10%

**HbA1c targets**

This is area which has changed in 2015

- individual targets should be agreed with patients to encourage motivation
- HbA1c should be checked every 3-6 months until stable, then 6 monthly
- NICE encourage us to consider relaxing targets on 'a case-by-case basis, with particular consideration for people who are older or frail, for adults with type 2 diabetes'
- in 2015 the guidelines changed so HbA1c targets are now dependent on treatment:

Lifestyle or single drug treatment

| Management of T2DM | HbA1c target |
|---|---|
| Lifestyle | 48 mmol/mol (6.5%) |
| Lifestyle + metformin | 48 mmol/mol (6.5%) |
| Includes any drug which may cause hypoglycaemia (e.g. lifestyle + sulfonylurea) | 53 mmol/mol (7.0%) |

Practical examples

- a patient is newly diagnosed with HbA1c and wants to try lifestyle treatment first. You agree a target of 48 mmol/mol (6.5%)
- you review a patient 6 months after starting metformin. His HbA1c is 51 mmol/mol (6.8%). You increase his metformin from 500mg bd to 500mg tds and reinforce lifestyle factors

Patient already on treatment

| Management of T2DM | HbA1c target |
|---|---|
| Already on one drug, but HbA1c has risen to 58 mmol/mol (7.5%) | 53 mmol/mol (7.0%) |

**Drug treatment**

The 2015 NICE guidelines introduced some changes into the management of type 2 diabetes. There are essentially two pathways, one for patients who can tolerate metformin, and one for those who can't:

**Tolerates metformin:**

- metformin is still first-line and should be offered if the HbA1c rises to 48 mmol/mol (6.5%)* on lifestyle interventions
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a second drug should be added from the following list:

- → sulfonylurea
- → gliptin
- → pioglitazone
- → SGLT-2 inhibitor
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then triple therapy with one of the following combinations should be offered:
- → metformin + gliptin + sulfonylurea
- → metformin + pioglitazone + sulfonylurea
- → metformin + sulfonylurea + SGLT-2 inhibitor
- → metformin + pioglitazone + SGLT-2 inhibitor
- → OR insulin therapy should be considered

Criteria for glucagon-like peptide1 (GLP1) mimetic (e.g. exenatide)

- if triple therapy is not effective, not tolerated or contraindicated then NICE advise that we consider combination therapy with metformin, a sulfonylurea and a glucagonlike peptide1 (GLP1) mimetic if:
- → BMI >= 35 kg/m² and specific psychological or other medical problems associated with obesity or
- → BMI < 35 kg/m² and for whom insulin therapy would have significant occupational implications or
- weight loss would benefit other significant obesityrelated comorbidities
- only continue if there is a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months

Practical examples

- you review an established type 2 diabetic on maximum dose metformin. Her HbA1c is 55 mmol/mol (7.2%). You do not add another drug as she has not reached the threshold of 58 mmol/mol (7.5%)
- a type 2 diabetic is found to have a HbA1c of 62 mmol/mol (7.8%) at annual review. They are currently on maximum dose metformin. You elect to add a sulfonylurea

**Cannot tolerate metformin or contraindicated**

- if the HbA1c rises to 48 mmol/mol (6.5%)* on lifestyle interventions, consider one of the following:
- → sulfonylurea
- → gliptin
- → pioglitazone
- if the HbA1c has risen to 58 mmol/mol (7.5%) then a one of the following combinations should be used:
- → gliptin + pioglitazone
- → gliptin + sulfonylurea
- → pioglitazone + sulfonylurea
- if despite this the HbA1c rises to, or remains above 58 mmol/mol (7.5%) then consider insulin therapy

Starting insulin

- metformin should be continued. In terms of other drugs NICE advice: 'Review the continued need for other blood glucose lowering therapies'
- NICE recommend starting with human NPH insulin (isophane, intermediate acting) taken at bed-time or twice daily according to need

**Risk factor modification**

Blood pressure

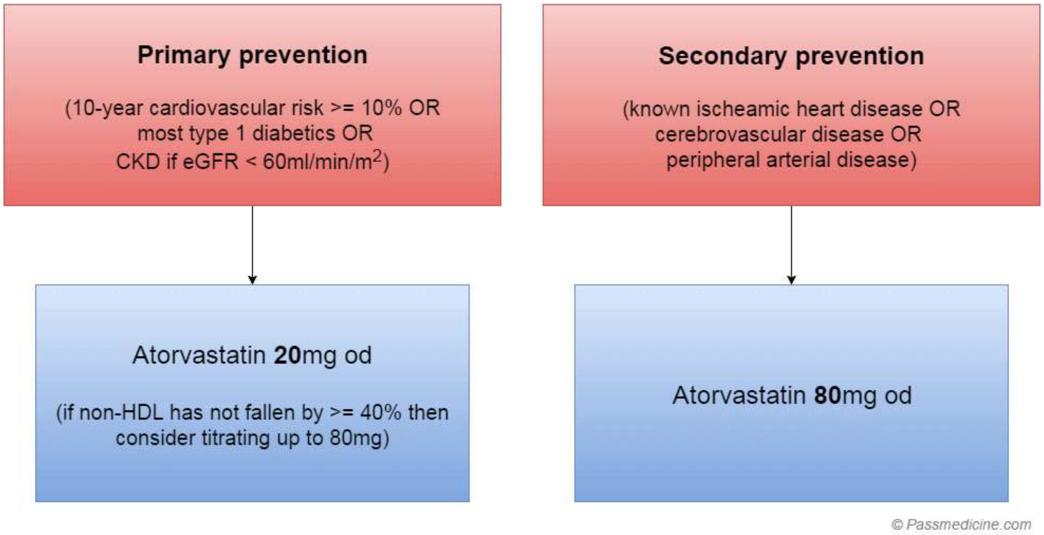
- target is < 140/80 mmHg (or < 130/80 mmHg if end-organ damage is present)
- ACE inhibitors are first-line

Antiplatelets

- should not be offered unless a patient has existing cardiovascular disease

Lipids

- following the 2014 NICE lipid modification guidelines only patients with a 10-year cardiovascular risk > 10% (using QRISK2) should be offered a statin. The first-line statin of choice is atorvastatin 20mg on


Primary prevention
(10-year cardiovascular risk >= 10% OR
most type 1 diabetics OR
CKD if eGFR < 60ml/min/m2)
Secondary prevention
(known ischeamic heart disease OR
cerebrovascular disease OR
peripheral arterial disease)
Atorvastatin 20mg od
(if non-HDL has not fallen by >= 40% then
consider titrating up to 80mg)
Atorvastatin 80mg od
© Passmedicine.com

Graphic showing choice of statin.

*this is a bit confusing because isn't the diagnostic criteria for T2DM HbA1c 48 mmol/mol (6.5%)? So shouldn't all patients be offered metformin at diagnosis? Our interpretation of this is that some patients upon diagnosis will elect to try lifestyle measures, which may reduce their HbA1c below this level. If it then rises to the diagnostic threshold again metformin should be offered

## T2DM MEDICATIONS

Drugs used

- sulphonylureas
- metformin
- alpha-glucosidase inhibitors (acarbose)
- glitazones
- insulin

## SULFONYLUREAS

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present. On a molecular level they bind to an ATP-dependent K+(KATP) channel on the cell membrane of pancreatic beta cells.

Common adverse effects

- hypoglycaemic episodes (more common with long-acting preparations such as chlorpropamide)
- weight gain

Rarer adverse effects

- hyponatraemia secondary to syndrome of inappropriate ADH secretion
- bone marrow suppression
- hepatotoxicity (typically cholestatic)
- peripheral neuropathy

Sulfonylureas should be avoided in breastfeeding and pregnancy.

## THIAZOLIDINEDIONES

Thiazolidinediones are a class of agents used in the treatment of type 2 diabetes mellitus. They are agonists to the PPAR-gamma receptor and reduce peripheral insulin resistance. Rosiglitazone was withdrawn in 2010 following concerns about the cardiovascular side-effect profile.

The PPAR-gamma receptor is an intracellular nuclear receptor. It's natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function.

Adverse effects

- weight gain
- liver impairment: monitor LFTs
- fluid retention - therefore contraindicated in heart failure. The risk of fluid retention is increased if the patient also takes insulin
- recent studies have indicated an increased risk of fractures

- bladder cancer: recent studies have shown an increased risk of bladder cancer in patients taking pioglitazone (hazard ratio 2.64)

# DIABETES MELLITUS: GLP-1 AND THE NEW DRUGS

A number of new drugs to treat diabetes mellitus have become available in recent years. Much research has focused around the role of glucagon-like peptide-1 (GLP-1), a hormone released by the small intestine in response to an oral glucose load

Whilst it is well known that insulin resistance and insufficient B-cell compensation occur other effects are also seen in type 2 diabetes mellitus (T2DM). In normal physiology an oral glucose load results in a greater release of insulin than if the same load is given intravenously - this known as the incretin effect. This effect is largely mediated by GLP-1 and is known to be decreased in T2DM.

Increasing GLP-1 levels, either by the administration of an analogue (glucagon-like peptide-1, GLP-1 mimetics, e.g. exenatide) or inhibiting its breakdown (dipeptidyl peptidase-4 ,DPP-4 inhibitors - the gliptins), is therefore the target of two recent classes of drug.

**Glucagon-like peptide-1 (GLP-1) mimetics (e.g. exenatide)**
Exenatide is an example of a glucagon-like peptide-1 (GLP-1) mimetic. These drugs increase insulin secretion and inhibit glucagon secretion. One of the major advances of GLP-1 mimetics is that they typically result in weight loss, in contrast to many medications such as insulin, sulfonylureas and thiazolidinediones. They are sometimes used in combination with insulin in T2DM to minimise weight gain.

Exenatide must be given by subcutaneous injection within 60 minutes before the morning and evening meals. It should not be given after a meal.

Liraglutide is the other GLP-1 mimetic currently available. One the main advantages of liraglutide over exenatide is that it only needs to be given once a day.

Both exenatide and liraglutide may be combined with metformin and a sulfonylurea. Standard release exenatide is also licensed to be used with basal insulin alone or with metformin. Please see the BNF for a more complete list of licensed indications.

NICE state the following:

Consider adding exenatide to metformin and a sulfonylurea if:

- *BMI >= 35 kg/m² in people of European descent and there are problems associated with high weight, or*
- *BMI < 35 kg/m² and insulin is unacceptable because of occupational implications or weight loss would benefit other comorbidities.*

NICE like patients to have achieved a 11 mmol/mol (1%) reduction in HbA1c and 3% weight loss after 6 months to justify the ongoing prescription of GLP-1 mimetics.

The major adverse effect of GLP-1 mimetics is nausea and vomiting. The Medicines and Healthcare products Regulatory Agency has issued specific warnings on the use of exenatide, reporting that is has been linked to severe pancreatitis in some patients.

**Dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g. Vildagliptin, sitagliptin)**
Key points
- oral preparation
- trials to date show that the drugs are relatively well tolerated with no increased incidence of hypoglycaemia
- do not cause weight gain

NICE guidelines on DPP-4 inhibitors
- NICE suggest that a DPP-4 inhibitor might be preferable to a thiazolidinedione if further weight gain would cause significant problems, a thiazolidinedione is contraindicated or the person has had a poor response to a thiazolidinedione

# SGLT-2 INHIBITORS

SGLT-2 inhibitors reversibly inhibit sodium-glucose co-transporter 2 (SGLT-2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

Examples include canagliflozin, dapagliflozin and empagliflozin.

Important adverse effects include
- urinary and genital infection (secondary to glycosuria). Fournier's gangrene has also been reported
- normoglycaemic ketoacidosis
- increased risk of lower-limb amputation: feet should be closely monitored

Patients taking SGLT-2 drugs often lose weight, which can be beneficial in type 2 diabetes mellitus.

# MEGLITINIDES

Meglitinides (e.g. repaglinide, nateglinide)
- increase pancreatic insulin secretion
- like sulfonylureas they bind to an ATP-dependent K+(KATP) channel on the cell membrane of pancreatic beta cells

- often used for patients with an erratic lifestyle
- adverse effects include weight gain and hypoglycaemia (less so than sulfonylureas)

# PREGNANCY: DIABETES MELLITUS

Diabetes mellitus may be a pre-existing problem or develop during pregnancy, gestational diabetes. It complicates up to 1 in 20 pregnancies. NICE estimate the following breakdown:
- 87.5% have gestational diabetes
- 7.5% have type 1 diabetes
- 5% have type 2 diabetes

Risk factors for gestational diabetes
- BMI of > 30 kg/m²
- previous macrosomic baby weighing 4.5 kg or above
- previous gestational diabetes
- first-degree relative with diabetes
- family origin with a high prevalence of diabetes (South Asian, black Caribbean and Middle Eastern)

Screening for gestational diabetes
- women who've previously had gestational diabetes: oral glucose tolerance test (OGTT) should be performed as soon as possible after booking and at 24-28 weeks if the first test is normal. NICE also recommend that early self-monitoring of blood glucose is an alternative to the OGTTs
- women with any of the other risk factors should be offered an OGTT at 24-28 weeks

Diagnostic thresholds for gestational diabetes
- these have recently been updated by NICE, gestational diabetes is diagnosed if either:
- fasting glucose is >= 5.6 mmol/l
- 2-hour glucose is >= 7.8 mmol/l

Management of gestational diabetes
- newly diagnosed women should be seen in a joint diabetes and antenatal clinic within a week
- women should be taught about selfmonitoring of blood glucose
- advice about diet (including eating foods with a low glycaemic index) and exercise should be given
- if the fasting plasma glucose level is < 7 mmol//l a trial of diet and exercise should be offered
- if glucose targets are not met within 1-2 weeks of altering diet/exercise metformin should be started
- if glucose targets are still not met insulin should be added to diet/exercise/metformin
- if at the time of diagnosis the fasting glucose level is >= 7 mmol/l insulin should be started
- if the plasma glucose level is between 6-6.9 mmol/l, and there is evidence of complications such as macrosomia or hydramnios, insulin should be offered

- glibenclamide should only be offered for women who cannot tolerate metformin or those who fail to meet the glucose targets with metformin but decline insulin treatment

Management of pre-existing diabetes
- weight loss for women with BMI of > 27 kg/m^2
- stop oral hypoglycaemic agents, apart from metformin, and commence insulin
- folic acid 5 mg/day from pre-conception to 12 weeks gestation
- aspirin 75mg/day from 12 weeks until the birth of the baby, to reduce the risk of pre-eclampsia
- detailed anomaly scan at 20 weeks including four-chamber view of the heart and outflow tracts
- tight glycaemic control reduces complication rates
- treat retinopathy as can worsen during pregnancy

**Targets for self monitoring of pregnant women (pre-existing and gestational diabetes)**

| Time | Target |
|---|---|
| Fasting | 5.3 mmol/l |
| 1 hour after meals | 7.8 mmol/l, or: |
| 2 hour after meals | 6.4 mmol/l |

# DIABETES MELLITUS: RAMADAN

We know that type 2 diabetes mellitus is more common in people of Asian ethnicity and a significant proportion of those patients in the UK will be Muslim. The BMJ published an excellent and comprehensive review of this issue in 20101.

It is important that we can give appropriate advice to Muslim patients to allow them safely observe their fast. This is particularly important from 2014 as Ramadan is due to fall in the long days of the summer months for several years henceforth.

Clearly it is a personal decision whether a patient decides to fast. It may however be worthwhile exploring the fact that people with chronic conditions are exempt from fasting or may be able to delay fasting to the shorter days of the winter months. It is however known that many Muslim patients with diabetes do not class themselves as having a chronic/serious condition which should exempt them from fasting. Around 79% of Muslim patients with type 2 diabetes mellitus fast Ramadan2.There is an excellent patient information leaflet from Diabetes UK and the Muslim Council of Britain which explores these options in more detail.

If a patient with type 2 diabetes mellitus does decide to fast:

- they should try and and eat a meal containing long-acting carbohydrates prior to sunrise (Suhoor)
- patients should be given a blood glucose monitor to allow them to check their glucose levels, particularly if they feel unwell
- for patients taking metformin the expert consensus is that the dose should be split one-third before sunrise (Suhoor) and two-thirds after sunset (Iftar)
- expert consensus also recommends switching once-daily sulfonylureas to after sunset. For patients taking twice-daily preparations such as gliclazide it is recommended that a larger proportion of the dose is taken after after sunset
- no adjustment is needed for patients taking pioglitazone

1. Management of people with diabetes wanting to fast during Ramadan BMJ 2010;340:c3053
2. Salti I et al. Results of the Epidemiology of Diabetes and Ramadan (EPIDIAR) study. Diabetes Care 2004;27:2306-11.

# DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) may be a complication existing type 1 diabetes mellitus or be the first presentation, accounting for around 6% of cases. Rarely, under conditions of extreme stress, patients with type 2 diabetes mellitus may also develop DKA.

Whilst DKA remains a serious condition mortality rates have decreased from 8% to under 1% in the past 20 years.

Pathophysiology
- DKA is caused by uncontrolled lipolysis (not proteolysis) which results in an excess of free fatty acids that are ultimately converted to ketone bodies

The most common precipitating factors of DKA are infection, missed insulin doses and myocardial infarction.

Features
- abdominal pain
- polyuria, polydipsia, dehydration
- Kussmaul respiration (deep hyperventilation)
- Acetone-smelling breath ('pear drops' smell)

**Diagnostic criteria**

| American Diabetes Association (2009) | Joint British Diabetes Societies (2013) |
|---|---|
| Key points | Key points |

| American Diabetes Association (2009) | Joint British Diabetes Societies (2013) |
|---|---|
| - glucose > 13.8 mmol/l<br>- pH < 7.30<br>- serum bicarbonate <18 mmol/l<br>- anion gap > 10<br>- ketonaemia | - glucose > 11 mmol/l or known diabetes mellitus<br>- pH < 7.3<br>- bicarbonate < 15 mmol/l<br>- ketones > 3 mmol/l or urine ketones ++ on dipstick |

Management

- fluid replacement: most patients with DKA are deplete around 5-8 litres. Isotonic saline is used initially. Please see an example fluid regime below.
- insulin: an intravenous infusion should be started at 0.1 unit/kg/hour. Once blood glucose is < 15 mmol/l an infusion of 5% dextrose should be started
- correction of hypokalaemia
- long-acting insulin should be continued, short-acting insulin should be stopped

**JBDS example of fluid replacement regime for patient with a systolic BP on admission 90mmHg and over**

| Fluid | Volume |
|---|---|
| 0.9% sodium chloride 1L | 1000ml over 1st hour |
| 0.9% sodium chloride 1L with potassium chloride | 1000ml over next 2 hours |
| 0.9% sodium chloride 1L with potassium chloride | 1000ml over next 2 hours |
| 0.9% sodium chloride 1L with potassium chloride | 1000ml over next 4 hours |
| 0.9% sodium chloride 1L with potassium chloride | 1000ml over next 4 hours |
| 0.9% sodium chloride 1L with potassium chloride | 1000ml over next 6 hours |

Please note that slower infusion may be indicated in young adults (aged 18-25 years) as they are at greater risk of cerebral oedema.

**JBDS potassium guidelines**

| Potassium level in first 24 hours (mmol/L) | Potassium replacement in mmol/L of infusion solution |
|---|---|
| Over 5.5 | Nil |
| 3.5-5.5 | 40 |
| Below 3.5 | Senior review as additional potassium needs to be given |

Complications of DKA and its treatment

- gastric stasis
- thromboembolism
- arrhythmias secondary to hyperkalaemia/iatrogenic hypokalaemia
- iatrogenic due to incorrect fluid therapy: cerebral oedema*, hypokalaemia, hypoglycaemia

- acute respiratory distress syndrome
- acute kidney injury

* children/young adults are particularly vulnerable to cerebral oedema following fluid resuscitation in DKA and often need 1:1 nursing to monitor neuro-observations, headache, irritability, visual disturbance, focal neurology etc. It usually occurs 4-12 hours following commencement of treatment but can present at any time. If there is any suspicion a CT head and senior review should be sought

# HYPEROSMOLAR HYPERGLYCAEMIC STATE

Hyperosmolar hyperglycaemic state (HHS) is a medical emergency which is extremely difficult to manage and has a significant associated mortality. Hyperglycaemia results in osmotic diuresis, severe dehydration, and electrolyte deficiencies. HHS typically presents in the elderly with type 2 diabetes mellitus (T2DM), however the incidence in younger adults is increasing. It can be the initial presentation of T2DM.

It is extremely important to differentiate HHS from diabetic ketoacidosis (DKA) as the management is different, and treatment of HHS with insulin (e.g. as part of a DKA protocol) can result in adverse outcomes. The first 24 hours of treatment is very labour intensive so these patients are best managed in either a medical high dependency unit.

HHS has a higher mortality than DKA and may be complicated by vascular complications such as myocardial infarction, stroke or peripheral arterial thrombosis. Seizures, cerebral oedema and central pontine myelinolysis (CPM) are uncommon but documented complications of HHS. Whilst DKA presents within hours of onset, HHS comes on over many days, and consequently the dehydration and metabolic disturbances are more extreme.

Pathophysiology

- Hyperglycaemia results in osmotic diuresis with associated loss of sodium and potassium
- Severe volume depletion results in a significant raised serum osmolarity (typically > than 320 mosmol/kg), resulting in hyperviscosity of blood.
- Despite these severe electrolyte losses and total body volume depletion, the typical patient with HHS, may not look as dehydrated as they are, because hypertonicity leads to preservation of intravascular volume.

Clinical features

- General: fatigue, lethargy, nausea and vomiting
- Neurological: altered level of consciousness, headaches, papilloedema, weakness

- Haematological: hyperviscosity (may result in myocardial infarctions, stroke and peripheral arterial thrombosis)
- Cardiovascular: dehydration, hypotension, tachycardia

Diagnosis

- Hypovolaemia
- Marked Hyperglycaemia (>30 mmol/L) without significant ketonaemia or acidosis
- Significantly raised serum osmolarity (> 320 mosmol/kg)
- Note: A precise definition of HHS does not exist, however the above 3 criteria are helpful in distinguishing between HHS and DKA. It is also important to remember that a mixed HHS / DKA picture can occur.

**Management**

The goals of management of HHS can be summarised as follows:

1. Normalise the osmolality (gradually)
2. Replace fluid and electrolyte losses
3. Normalise blood glucose (gradually)

Fluid replacement

- Fluid losses in HHS are estimated to be between 100 - 220 ml/kg (e.g. 10-22 litres in an individual weighing 100 kg).
- The rate of rehydration will be determined by assessing the combination of initial severity and any pre-existing co-morbidities (e.g. heart failure and chronic kidney disease). Caution is needed, particularly in the elderly, where too rapid rehydration may precipitate heart failure but insufficient may fail to reverse an acute kidney injury.
- Intravenous (IV) 0.9% sodium chloride solution is the first line fluid for restoring total body fluid.
- It is important to remember that isotonic 0.9% sodium chloride solution is already relatively hypotonic compared to the serum in someone with HHS. Therefore in most cases it is very effective at restoring normal serum osmolarity.
- If the serum osmolarity is not declining despite positive balance with 0.9% sodium chloride, then the fluid should be switched to 0.45% sodium chloride solution which is more hypotonic relative to the HHS patients serum osmolarity
- IV fluid replacement should aim to achieve a positive balance of 3-6 litres by 12 hours and the remaining replacement of estimated fluid losses within the next 12 hours.
- Existing guidelines encourage vigorous initial fluid replacement and this alone (without insulin) will result in a gradual decline in plasma glucose and serum osmolarity. A rapid decline is potentially harmful (see below) therefore insulin should NOT be used in the first instance unless there is significant ketonaemia or acidosis
- The aim of treatment should be to replace approximately 50% of estimated fluid loss within the first 12 hours and the remainder in the following 12 hours. However this is just a guide, and clinical judgement should be applied, particularly in patient with co-morbidities such as heart failure and chronic kidney disease (which may limit the speed of correction).

Monitoring response to treatment

- The key parameter in managing HHS is the osmolality to which glucose and sodium are the main contributors. Rapid changes of serum osmolarity are dangerous and can result in cardiovascular collapse and central pontine myelinolysis (CPM).
- Guidelines suggest that serum osmolarity, sodium and glucose levels should be plotted on a graph to permit appreciation of the rate of change. They should be plotted hourly initially.
- Not all laboratories have readily available access to serum osmolarity measurements. If not available then a calculated osmolarity can be estimated with 2Na + glucose + urea
- Fluid replacement alone (without insulin) will gradually lower blood glucose which will reduce osmolality
- A reduction of serum osmolarity will cause a shift of water into the intracellular space. This inevitably results in a rise in serum sodium (a fall in blood glucose of 5.5 mmol/L will result in a 2.4 mmol/L rise in sodium). This is not necessarily an indication to give hypotonic solutions. If the inevitable rise in serum Na+ is much greater than 2.4 mmol/L for each 5.5 mmol/L fall in blood glucose this would suggest insufficient fluid replacement. Rising sodium is only a concern if the osmolality is NOT declining concurrently.
- Rapid changes must be avoided. A safe rate of fall of plasma glucose of between 4 and 6 mmol/hr is recommended. The rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours.
- A target blood glucose of between 10 and 15 mmol/L is a reasonable goal.
- Complete normalisation of electrolytes and osmolality may take up to 72 hours.

Insulin

- Fluid replacement alone with 0.9% sodium chloride solution will result in a gradual decline of blood glucose and osmolarity
- Because most patients with HHS are insulin sensitive (e.g. it usually occurs in T2DM), administration of insulin can result in a rapid decline of serum glucose and thus osmolarity.
- Insulin treatment prior to adequate fluid replacement may result in cardiovascular collapse as the water moves out of the intravascular space, with a resulting decline in intravascular volume.
- A steep decline in serum osmolarity may also precipitate CPM.
- Measurement of ketones is essential for determining if insulin is required.
- If significant ketonaemia is present (3β-hydroxy butyrate is more than 1 mmol/L) this indicates relative hypoinsulinaemia and insulin should be started at time zero (e.g. mixed DKA / HHS picture). The recommended insulin dose is a fixed rate intravenous insulin infusion given at 0.05 units per kg per hour.
- If significant ketonaemia is not present (3β-hydroxy butyrate is less than 1 mmol/L) then do NOT start insulin.

Potassium

- Patients with HHS are potassium deplete but less acidotic than those with DKA so potassium shifts are less pronounced
- Hyperkalaemia can be present with acute kidney injury
- Patients on diuretics may be profoundly hypokalaemic

- Potassium should be replaced or omitted as required

# HYPOGLYCAEMIA

Causes
- insulinoma - increased ratio of proinsulin to insulin
- self-administration of insulin/sulphonylureas
- liver failure
- Addison's disease
- alcohol

Other possible causes in children
- nesidioblastosis - beta cell hyperplasia

Physiological response to hypoglycaemia
- hormonal response: the first response of the body is decreased insulin secretion. This is followed by increased glucagon secretion. Growth hormone and cortisol are also released but later
- sympathoadrenal response: increased catecholamine-mediated (adrenergic) and acetylcholine-mediated (cholinergic) neurotransmission in the peripheral autonomic nervous system and in the central nervous system

# DIABETIC NEUROPATHY

Diabetes typically leads to sensory loss and not motor loss in peripheral neuropathy. Painful diabetic neuropathy is a common problem in clinical practice.

NICE updated it's guidance on the management of neuropathic pain in 2013. Diabetic neuropathy is now managed in the same way as other forms of neuropathic pain:
- first-line treatment: amitriptyline, duloxetine, gabapentin or pregabalin
- if the first-line drug treatment does not work try one of the other 3 drugs
- tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- pain management clinics may be useful in patients with resistant problems

**Gastrointestinal autonomic neuropathy**

Gastroparesis
- symptoms include erratic blood glucose control, bloating and vomiting
- management options include metoclopramide, domperidone or erythromycin (prokinetic agents)

Chronic diarrhoea
- often occurs at night

Gastro-oesophageal reflux disease
- caused by decreased lower esophageal sphincter (LES) pressure

# DIABETIC FOOT DISEASE

Diabetic foot disease is an important complication of diabetes mellitus which should be screen for on a regular basis. NICE produced guidelines relating to diabetic foot disease in 2015.

It occurs secondary to two main factors:
- neuropathy: resulting in loss of protective sensation (e.g. not noticing a stone in the shoe), Charcot's arthropathy, dry skin
- peripheral arterial disease: diabetes is a risk factor for both macro and microvascular ischaemia

Presentations
- neuropathy: loss of sensation
- ischaemia: absent foot pulses, reduced ankle-brachial pressure index (ABPI), intermittent claudication
- complications: calluses, ulceration, Charcot's arthropathy, cellulitis, osteomyelitis, gangrene

All patients with diabetes should be screened for diabetic foot disease on at least an annual basis
- screening for ischaemia: done by palpating for both the dorsalis pedis pulse and posterial tibial artery pulse
- screening for neuropathy: a 10 g monofilament is used on various parts of the sole of the foot

NICE recommend that we risk stratify patients:

| Low risk | Moderate risk | High risk |
|---|---|---|
| • no risk factors except callus alone | • deformity or<br>• neuropathy or<br>• non-critical limb ischaemia. | • previous ulceration or<br>• previous amputation or<br>• on renal replacement therapy or<br>• neuropathy and non-critical limb ischaemia together or<br>• neuropathy in combination with callus and/or deformity or<br>• non-critical limb ischaemia in combination with callus and/or deformity. |

All patients who are moderate or high risk (I.e. any problems other than simple calluses) should be followed up regularly by the local diabetic foot centre.

# DVLA: DIABETES MELLITUS

Until recently people with diabetes who used insulin could not hold a HGV licence. The DVLA changed the rules in October 2011. The following standards need to be met (and also apply to patients using other hypoglycaemic inducing drugs such as sulfonylureas):

- there has not been any severe hypoglycaemic event in the previous 12 months
- the driver has full hypoglycaemic awareness
- the driver must show adequate control of the condition by regular blood glucose monitoring*, at least twice daily and at times relevant to driving
- the driver must demonstrate an understanding of the risks of hypoglycaemia
- here are no other debarring complications of diabetes

From a practical point of view patients on insulin who want to apply for a Group 2 (HGV) licence need to complete a VDIAB1I form.

Other specific points for group 1 drivers:

- if on insulin then patient can drive a car as long as they have hypoglycaemic awareness, not more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months and no relevant visual impairment. Drivers are normally contacted by DVLA
- if on tablets or exenatide no need to notify DVLA. If tablets may induce hypoglycaemia (e.g. sulfonylureas) then there must not have been more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months
- if diet controlled alone then no requirement to inform DVLA

*to demonstrate adequate control, the Secretary of State's Honorary Medical Advisory Panel on Diabetes Mellitus has recommended that applicants will need to have used blood glucose meters with a memory function to measure and record blood glucose levels for at least 3 months prior to submitting their application

# METABOLIC SYNDROME

Unfortunately there are a number of competing definitions of the metabolic syndrome around at the present time. It is thought that the key pathophysiological factor is insulin resistance.

SIGN recommend using criteria similar to those from the American Heart Association. The similarity of the International Diabetes Federation criteria should be noted. For a diagnosis of metabolic syndrome at least 3 of the following should be identified:

- elevated waist circumference: men > 102 cm, women > 88 cm
- elevated triglycerides: > 1.7 mmol/L
- reduced HDL: < 1.03 mmol/L in males and < 1.29 mmol/L in females
- raised blood pressure: > 130/85 mmHg, or active treatment of hypertension
- raised fasting plasma glucose > 5.6 mmol/L, or previously diagnosed type 2 diabetes

The International Diabetes Federation produced a consensus set of diagnostic criteria in 2005, which are now widely in use. These require the presence of central obesity (defined as waist circumference > 94cm for Europid men and > 80cm for Europid women, with ethnicity specific values for other groups) plus any two of the following four factors:

- raised triglycerides level: > 1.7 mmol/L, or specific treatment for this lipid abnormality
- reduced HDL cholesterol: < 1.03 mmol/L in males and < 1.29 mmol/L in females, or specific treatment for this lipid abnormality
- raised blood pressure: > 130/85 mm Hg, or active treatment of hypertension
- raised fasting plasma glucose > 5.6 mmol/L, or previously diagnosed type 2 diabetes

In 1999 the World Health Organization produced diagnostic criteria which required the presence of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, AND two of the following:

- blood pressure: > 140/90 mmHg
- dyslipidaemia: triglycerides: > 1.695 mmol/L and/or high-density lipoprotein cholesterol (HDL-C) < 0.9 mmol/L (male), < 1.0 mmol/L (female)
- central obesity: waist:hip ratio > 0.90 (male), > 0.85 (female), and/or body mass index > 30 kg/m2
- microalbuminuria: urinary albumin excretion ratio > 20 mg/min or albumin:creatinine ratio > 30 mg/g

Other associated features include:

- raised uric acid levels
- non-alcoholic fatty liver disease
- polycystic ovarian syndrome

# REMNANT HYPERLIPIDAEMIA

Overview

- rare cause of mixed hyperlipidaemia (raised cholesterol and triglyceride levels)
- also known as Fredrickson type III hyperlipidaemia, broad-beta disease and dysbetalipoproteinaemia
- associated with apo-e2 homozygosity
- high incidence of ischaemic heart disease and peripheral vascular disease
- thought to be caused by impaired removal of intermediate density lipoprotein from the circulation by the liver

Features

- yellow palmar creases
- palmer xanthomas
- tuberous xanthomas

Management

- fibrates are first line treatment

# OBESITY: THERAPEUTIC OPTIONS

The management of obesity consists of a step-wise approach:

- conservative: diet, exercise
- medical
- surgical

Orlistat is a pancreatic lipase inhibitor used in the management of obesity. Adverse effects include faecal urgency/incontinence and flatulence. A lower dose version is now available without prescription ('Alli'). NICE have defined criteria for the use of orlistat. It should only be prescribed as part of an overall plan for managing obesity in adults who have:

- BMI of 28 kg/m^2 or more with associated risk factors, or
- BMI of 30 kg/m^2 or more
- continued weight loss e.g. 5% at 3 months
- orlistat is normally used for < 1 year

# THYROID DISORDERS: A VERY BASIC INTRODUCTION

Disorders of thyroid function are very commonly encountered in clinical practice. Around 2% of the UK population has hypothyroidism (an under active thyroid gland) whilst around 1% have thyrotoxicosis (an over active gland). Both hypothyroidism and hyperthyrodism (also known as thyrotoxicosis) are around 10 times more common in women than men.

**Structure and function**

The thyroid gland is one of the largest endocrine organs in the body. It is a bi-lobed structure which is found in the anterior neck. As with many endocrine organs, it is part of a hypothalamus-pituitary-end organ system with negative feedback cycles to maintain normal circulating levels of the hormone, in this case thyroxine and triiodothyronine.

On a simple level the hypothalamus secretes thyrotropin-releasing hormone (TRH) which stimulates the anterior pituitary to secrete thyroid-stimulating hormone (TSH). This then acts on the thyroid gland increasing the production of thyroxine (T4) and triiodothyronine (T3), the two main thyroid hormones. These then act on a wide variety of tissues, helping to regulate the use of energy sources, protein synthesis, and controls the body's sensitivity to other hormones.

**How are thyroid problems classified?**

Hypothyroidism may be classified as follows:

- primary hypothyroidism: there is a problem with the thyroid gland itself, for example an autoimmune disorder affecting thyroid tissue (see below)
- secondary hypothyroidism: usually due to a disorder with the pituitary gland (e.g.pituitary apoplexy) or a lesion compressing the pituitary gland
- congenital hypothyroidism: due to a problem with thyroid dysgenesis or thyroid dyshormonogenesis

Whilst there are a number of causes thyrotoxicosis the vast majority are primary in nature. Congenital thyrotoxicosis is not seen and secondary hyperthyroidism is rare, account for less than 1% of cases.

**What causes thyroid problems?**

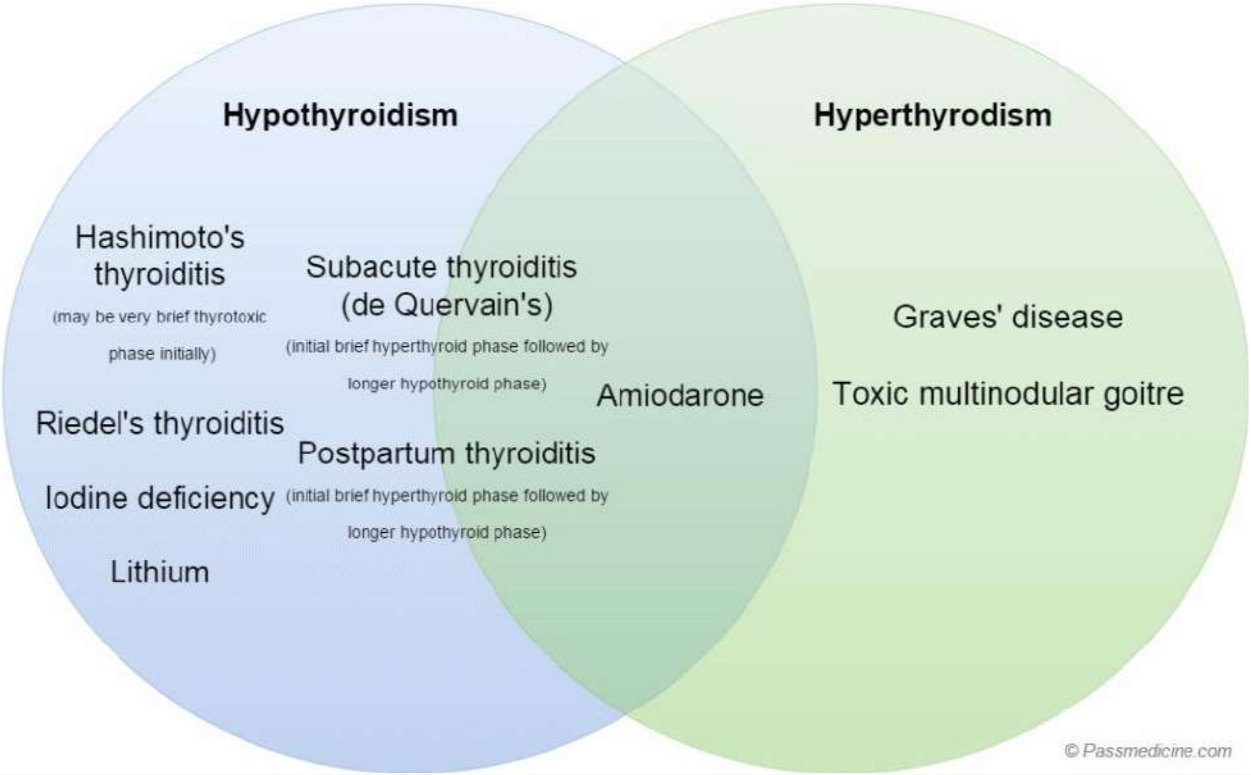
The majority of thyroid problems seen in the developed world are a consequence of autoimmunity.

The table below shows the different autoimmune problems which cause thyroid dysfunction:

| | Hypothyroidism | Thyrotoxicosis |
|---|---|---|
| **Most common cause** | Hashimoto's thyroiditis<br>• most common cause in the developed world | Graves' disease<br>• most common cause of thyrotoxicosis |

| | Hypothyroidism | Thyrotoxicosis |
|---|---|---|
| | • autoimmune disease, associated with type 1 diabetes mellitus, Addison's or pernicious anaemia<br>• may cause transient thyrotoxicosis in the acute phase<br>• 5-10 times more common in women | • as well as typically features of thyrotoxicosis other features may be seen including thyroid eye disease |
| **Other causes** | Subacute thyroiditis (de Quervain's)<br>• associated with a painful goitre and raised ESR<br>Riedel thyroiditis<br>• fibrous tissue replacing the normal thyroid parenchyma<br>• causes a painless goitre<br>Postpartum thyroiditis<br>Drugs<br>• lithium<br>• amiodarone<br>Iodine deficiency<br>• the most common cause of hypothyroidism in the developing world | Toxic multinodular goitre<br>• autonomously functioning thyroid nodules that secrete excess thyroid hormones<br>Drugs<br>• amiodarone |

It should be remembered that a lot of the conditions mentioned above don't always cause either hypothyroidism or hyperthyroidism, there is sometimes some overlap, as shown below:


Hypothyroidism
Hyperthyrodism
Hashimoto's thyroiditis
(may be very brief thyrotoxic phase initially)
Riedel's thyroiditis
Iodine deficiency
Lithium
Subacute thyroiditis (de Quervain's)
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Postpartum thyroiditis
(initial brief hyperthyroid phase followed by longer hypothyroid phase)
Amiodarone
Graves' disease
Toxic multinodular goitre
© Passmedicine.com

Venn diagram showing how different causes of thyroid dysfunction may manifest. Note how many causes of hypothyroidism may have an initial thyrotoxic phase.

**Symptoms and signs**

Thyroid disorders can present in a large variety of ways. Often (but not always) the symptoms present are the opposite depending on whether the thyroid gland is under or over active, for example hypothyroidism may result in weight gain whilst thyrotoxicosis normally leads to weight loss

| Feature | Hypothyroidism | Thyrotoxicosis |
|---|---|---|
| **General** | **Weight gain**<br>**Lethargy**<br>**Cold intolerance** | **Weight loss**<br>'Manic', restlessness<br>Heat intolerance |
| **Cardiac** | - | **Palpitations**, may even provoke arrhythmias e.g. atrial fibrillation |
| **Skin** | Dry (anhydrosis), cold, yellowish skin<br>Non-pitting oedema (e.g. hands, face)<br>Dry, coarse scalp hair, loss of lateral aspect of eyebrows | Increased sweating<br>Pretibial myxoedema: erythematous, oedematous lesions above the lateral malleoli<br>Thyroid acropachy: clubbing |
| **Gastrointestinal** | Constipation | Diarrhoea |
| **Gynaecological** | Menorrhagia | Oligomenorrhea |

| Feature | Hypothyroidism | Thyrotoxicosis |
|---|---|---|
| **Neurological** | Decreased deep tendon reflexes<br>Carpal tunnel syndrome | **Anxiety**<br>**Tremor** |

**Investigations and diagnosis**

The principle investigation is 'thyroid function tests', or TFTs for short:

- these primarily look at serum TSH and T4 levels
- T3 can be measured but is only useful clinically in a small number of cases
- remember that TSH and T4 levels will often be 'opposite' in cases of primary hypo- or hyperthyroidism. For example in hypothyroidism the T4 level is low (i.e. not enough thyroxine) but the TSH level is high, because the hypothalamus/pituitary has detected low levels of T4 and is trying to get the thyroid gland to produce more
- TSH levels are more sensitive than T4 levels for monitoring patients with existing thyroid problems and are often used to guide treatment

The table below shows how thyroid function tests are interpreted:

| Diagnosis | TSH | Free T4 | Notes |
|---|---|---|---|
| Thyrotoxicosis (e.g. Graves' disease) | Low | High | |
| Primary hypothyroidism (e.g. Hashimoto's thyroiditis) | High | Low | |
| Secondary hypothyroidism | Low | Low | |
| Sick euthyroid syndrome | Low | Low | Common in hospital inpatients. Changes are reversible upon recovery from the systemic illness and no treatment is usually needed |
| Subclinical hypothyroidism | High | Normal | This is a common finding and represents patients who are 'on the way' to developing hypothyroidism but still have normal thyroxine levels. Note how the TSH levels, as mentioned above, are a more sensitive and early marker of thyroid problems |
| Poor compliance with thyroxine | High | Normal | Patients who are poorly compliant may only take their thyroxine in the days before a routine blood test. The thyroxine levels are hence normal but the TSH 'lags' and reflects longer term low thyroxine levels |

A number of thyroid autoantibodies can be tested for (remember the majority of thyroid disorders are autoimmune). The 3 main types are:

- Anti-thyroid peroxidase (anti-TPO) antibodies
- TSH receptor antibodies
- Thyroglobulin antibodies

There is significant overlap between the type of antibodies present and particular diseases, but generally speaking TSH receptor antibodies are present in around 90-100% of patients with Graves' disease and anti-TPO antibodies are seen in around 90% of patients with Hashimoto's thyroiditis.

Other tests include:

- nuclear scintigraphy; toxic multinodular goitre reveals patchy uptake

**Treatment**

This clearly depends on the cause. For patients with hypothyrodism thyroxine is given in the form of levothyroxine to replace the underlying deficiency.

Patients with thyrotoxicosis may be treated with:

- propranolol: this is often used at the time of diagnosis to control thyrotoxic symptoms such as tremor
- carbimazole: blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin → reducing thyroid hormone production. Agranulocytosis is an important adverse effect to be aware of
- radioiodine treatment

# THYROID FUNCTION TESTS

The interpretation of thyroid function tests is usually straightforward:

| Diagnosis | TSH | Free T4 | Notes |
|---|---|---|---|
| Thyrotoxicosis (e.g. Graves' disease) | Low | High | In T3 thyrotoxicosis the free T4 will be normal |
| Primary hypothyroidism (primary atrophic hypothyroidism) | High | Low | |
| Secondary hypothyroidism | Low | Low | Replacement steroid therapy is required prior to thyroxine |
| Sick euthyroid syndrome* | Low** | Low | Common in hospital inpatients<br>T3 is particularly low in these patients |
| Subclinical hypothyroidism | High | Normal | |
| Poor compliance with thyroxine | High | Normal | |
| Steroid therapy | Low | Normal | |

*now referred to as non-thyroidal illness

**TSH may be normal in some cases

# SICK EUTHYROID SYNDROME

In sick euthyroid syndrome (now referred to as non-thyroidal illness) it is often said that everything (TSH, thyroxine and T3) is low. In the majority of cases however the TSH level is within the >normal range (inappropriately normal given the low thyroxine and T3).

Changes are reversible upon recovery from the systemic illness and hence no treatment is usually needed.

## SUBCLINICAL HYPOTHYROIDISM

Basics

- TSH raised but T3, T4 normal
- no obvious symptoms

Significance

- risk of progressing to overt hypothyroidism is 2-5% per year (higher in men)
- risk increased by the presence of thyroid autoantibodies

**Management**

Not all patients require treatment. NICE Clinical Knowledge Summaries (CKS) have produced guidelines. Note that not all patients will fall within the age boundaries given and hence these are guidelines in the broader sense.

TSH is between 4 - 10mU/L and the free thyroxine level is within the normal range

- if < 65 years with symptoms suggestive of hypothyroidism, give a trial of levothyroxine. If there is no improvement in symptoms, stop levothyroxine
- 'in older people (especially those aged over 80 years) follow a 'watch and wait' strategy, generally avoiding hormonal treatment'
- if asymptomatic people, observe and repeat thyroid function in 6 months

TSH is > 10mU/L and the free thyroxine level is within the normal range

- start treatment (even if asymptomatic) with levothyroxine if <= 70 years
- 'in older people (especially those aged over 80 years) follow a 'watch and wait' strategy, generally avoiding hormonal treatment'

## HYPOTHYROIDISM: CAUSES

Hypothyroidism affects around 1-2% of women in the UK and is around 5-10 times more common in females than males.

**Primary hypothyroidism**

Hashimoto's thyroiditis

- most common cause
- autoimmune disease, associated with IDDM, Addison's or pernicious anaemia
- may cause transient thyrotoxicosis in the acute phase
- 5-10 times more common in women

Subacute thyroiditis (de Quervain's)

Riedel thyroiditis

After thyroidectomy or radioiodine treatment

Drug therapy (e.g. lithium, amiodarone or anti-thyroid drugs such as carbimazole)

Dietary iodine deficiency

**Secondary hypothyroidism (rare)**
From pituitary failure

Other associated conditions
- Down's syndrome
- Turner's syndrome
- coeliac disease

# HYPOTHYROIDISM: FEATURES

General
- Weight gain
- Lethargy
- Cold intolerance

Skin
- Dry (anhydrosis), cold, yellowish skin
- Non-pitting oedema (e.g. hands, face)
- Dry, coarse scalp hair, loss of lateral aspect of eyebrows

Gastrointestinal
- Constipation

Gynaecological
- Menorrhagia

Neurological
- Decreased deep tendon reflexes
- Carpal tunnel syndrome

A hoarse voice is also occasionally noted.

## HYPOTHYROIDISM: MANAGEMENT

Key points
- initial starting dose of levothyroxine should be lower in elderly patients and those with ischaemic heart disease. The BNF recommends that for patients with cardiac disease, severe hypothyroidism or patients over 50 years the initial starting dose should be 25mcg od with dose slowly titrated. Other patients should be started on a dose of 50-100mcg od
- following a change in thyroxine dose thyroid function tests should be checked after 8-12 weeks
- the therapeutic goal is 'normalisation' of the thyroid stimulating hormone (TSH) level. As the majority of unaffected people have a TSH value 0.5-2.5 mU/l it is now thought preferable to aim for a TSH in this range
- women with established hypothyroidism who become pregnant should have their dose increased 'by at least 25-50 micrograms levothyroxine'* due to the increased demands of pregnancy. The TSH should be monitored carefully, aiming for a low-normal value
- there is no evidence to support combination therapy with levothyroxine and liothyronine

Side-effects of thyroxine therapy
- hyperthyroidism: due to over treatment
- reduced bone mineral density
- worsening of angina
- atrial fibrillation

Interactions
- iron, calcium carbonate
  - absorption of levothyroxine reduced, give at least 4 hours apart

*source: NICE Clinical Knowledge Summaries

## HASHIMOTO'S THYROIDITIS

Hashimoto's thyroiditis (chronic autoimmune thyroiditis) is an autoimmune disorder of the thyroid gland. It is typically associated with hypothyroidism although there may be a transient thyrotoxicosis in the acute phase. It is 10 times more common in women

Features
- features of hypothyroidism
- goitre: firm, non-tender

- anti-thyroid peroxidase (TPO) and also anti-thyroglobulin (Tg) antibodies

Associations
- other autoimmune conditions e.g. coeliac disease, type 1 diabetes mellitus, vitiligo
- Hashimoto's thyroiditis is associated with the development of MALT lymphoma

# SUBACUTE (DE QUERVAIN'S) THYROIDITIS

Subacute thyroiditis (also known as De Quervain's thyroiditis and subacute granulomatous thyroiditis) is thought to occur following viral infection and typically presents with hyperthyroidism.

There are typically 4 phases;
- phase 1 (lasts 3-6 weeks): hyperthyroidism, painful goitre, raised ESR
- phase 2 (1-3 weeks): euthyroid
- phase 3 (weeks - months): hypothyroidism
- phase 4: thyroid structure and function goes back to normal

Investigations
- thyroid scintigraphy: globally reduced uptake of iodine-131

Management
- usually self-limiting - most patients do not require treatment
- thyroid pain may respond to aspirin or other NSAIDs
- in more severe cases steroids are used, particularly if hypothyroidism develops

# RIEDEL'S THYROIDITIS

Riedel's thyroiditis is a rare cause of hypothyroidism characterised by dense fibrous tissue replacing the normal thyroid parenchyma. On examination a hard, fixed, painless goitre is noted. It is usually seen in middle-aged women. It is associated with retroperitoneal fibrosis.

# SUBCLINICAL HYPERTHYROIDISM

Subclinical hyperthyroidism is an entity which is gaining increasing recognition. It is defined as:
- normal serum free thyroxine and triiodothyronine levels
- with a thyroid stimulating hormone (TSH) below normal range (usually < 0.1 mu/l)

Causes
- multinodular goitre, particularly in elderly females

- excessive thyroxine may give a similar biochemical picture

The importance in recognising subclinical hyperthyroidism lies in the potential effect on the cardiovascular system (atrial fibrillation) and bone metabolism (osteoporosis). It may also impact on quality of life and increase the likelihood of dementia

Management
- TSH levels often revert to normal - therefore levels must be persistently low to warrant intervention
- a reasonable treatment option is a therapeutic trial of low-dose antithyroid agents for approximately 6 months in an effort to induce a remission

# THYROTOXICOSIS: CAUSES AND INVESTIGATION

Graves' disease accounts for around 50-60% of cases of thyrotoxicosis.

Causes
- Graves' disease
- toxic nodular goitre
- acute phase of subacute (de Quervain's) thyroiditis
- acute phase of post-partum thyroiditis
- acute phase of Hashimoto's thyroiditis (later results in hypothyroidism)
- amiodarone therapy

Investigation
- TSH down, T4 and T3 up
- thyroid autoantibodies
- other investigations are not routinely done but includes isotope scanning

# GRAVES' DISEASE: FEATURES

Graves' disease is the most common cause of thyrotoxicosis. It is typically seen in women aged 30-50 years.

Features
- typical features of thyrotoxicosis
- specific signs limited to Grave's (see below)

Features seen in Graves' but not in other causes of thyrotoxicosis
- eye signs (30% of patients)
  - exophthalmos

  - ophthalmoplegia
- pretibial myxoedema
- thyroid acropachy, a triad of:
  - digital clubbing
  - soft tissue swelling of the hands and feet
  - periosteal new bone formation

Autoantibodies
- TSH receptor stimulating antibodies (90%)
- anti-thyroid peroxidase antibodies (75%)

# GRAVES' DISEASE: MANAGEMENT

Despite many trials there is no clear guidance on the optimal management of Graves' disease. Treatment options include titration of anti-thyroid drugs (ATDs, for example carbimazole), block-and-replace regimes, radioiodine treatment and surgery. Propranolol is often given initially to block adrenergic effects

ATD titration
- carbimazole is started at 40mg and reduced gradually to maintain euthyroidism
- typically continued for 12-18 months
- patients following an ATD titration regime have been shown to suffer fewer side-effects than those on a block-and-replace regime

Block-and-replace
- carbimazole is started at 40mg
- thyroxine is added when the patient is euthyroid
- treatment typically lasts for 6-9 months

The major complication of carbimazole therapy is agranulocytosis

Radioiodine treatment
- contraindications include pregnancy (should be avoided for 4-6 months following treatment) and age < 16 years. Thyroid eye disease is a relative contraindication, as it may worsen the condition
- the proportion of patients who become hypothyroid depends on the dose given, but as a rule the majority of patient will require thyroxine supplementation after 5 years

# THYROID EYE DISEASE

Thyroid eye disease affects between 25-50% of patients with Graves' disease.

Pathophysiology

- it is thought to be caused by an autoimmune response against an autoantigen, possibly the TSH receptor → retro-orbital inflammation
- the inflammation results in glycosaminoglycan and collagen deposition in the muscles

Prevention

- smoking is the most important modifiable risk factor for the development of thyroid eye disease
- radioiodine treatment may increase the inflammatory symptoms seen in thyroid eye disease. In a recent study of patients with Graves' disease around 15% developed, or had worsening of, eye disease. Prednisolone may help reduce the risk

Features

- the patient may be eu-, hypo- or hyperthyroid at the time of presentation
- exophthalmos
- conjunctival oedema
- optic disc swelling
- ophthalmoplegia
- inability to close the eyelids may lead to sore, dry eyes. If severe and untreated patients can be at risk of exposure keratopathy

Management

- topical lubricants may be needed to help prevent corneal inflammation caused by exposure
- steroids
- radiotherapy
- surgery

**Monitoring patients with established thyroid eye disease**

For patients with established thyroid eye disease the following symptoms/signs should indicate the need for urgent review by an ophthalmologist (see EUGOGO guidelines):

- unexplained deterioration in vision
- awareness of change in intensity or quality of colour vision in one or both eyes
- history of eye suddenly 'popping out' (globe subluxation)
- obvious corneal opacity
- cornea still visible when the eyelids are closed
- disc swelling

# CARBIMAZOLE

Carbimazole is used in the management of thyrotoxicosis. It is typically given in high doses for 6 weeks until the patient becomes euthyroid before being reduced.

Mechanism of action

- blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin → reducing thyroid hormone production
- in contrast propylthiouracil as well as this central mechanism of action also has a peripheral action by inhibiting 5'-deiodinase which reduces peripheral conversion of T4 to T3

Adverse effects

- agranulocytosis
- crosses the placenta, but may be used in low doses during pregnancy

# TOXIC MULTINODULAR GOITRE

Toxic multinodular goitre describes a thyroid gland that contains a number of autonomously functioning thyroid nodules resulting in hyperthyroidism.

Nuclear scintigraphy reveals patchy uptake.

The treatment of choice is radioiodine therapy.

# PREGNANCY: THYROID PROBLEMS

In pregnancy, there is an increase in the levels of thyroxine-binding globulin (TBG). This causes an increase in the levels of total thyroxine but does not affect the free thyroxine level.

**Thyrotoxicosis**

Untreated thyrotoxicosis increases the risk of fetal loss, maternal heart failure and premature labour

Graves' disease is the most common cause of thyrotoxicosis in pregnancy. It is also recognised that activation of the TSH receptor by HCG may also occur - often termed transient gestational hyperthyroidism. HCG levels will fall in the second and third trimester

Management

- propylthiouracil has traditionally been the antithyroid drug of choice
- however, propylthiouracil is associated with an increased risk of severe hepatic injury
- therefore NICE Clinical Knowledge Summaries advocate the following: *'Propylthiouracil is used in the first trimester of pregnancy in place of carbimazole, as the latter drug may be associated with an increased risk of congenital abnormalities. At the beginning of the second trimester, the woman should be switched back to carbimazole'*
- maternal free thyroxine levels should be kept in the upper third of the normal reference range to avoid fetal hypothyroidism

- thyrotrophin receptor stimulating antibodies should be checked at 30-36 weeks gestation - helps to determine the risk of neonatal thyroid problems
- block-and-replace regimes should not be used in pregnancy
- radioiodine therapy is contraindicated

**Hypothyroidism**
Key points
- thyroxine is safe during pregnancy
- serum thyroid stimulating hormone measured in each trimester and 6-8 weeks post-partum
- some women require an increased dose of thyroxine during pregnancy
- breast feeding is safe whilst on thyroxine

# SKIN DISORDERS ASSOCIATED WITH THYROID DISEASE

Skin manifestations of hypothyroidism
- dry (anhydrosis), cold, yellowish skin
- non-pitting oedema (e.g. hands, face)
- dry, coarse scalp hair, loss of lateral aspect of eyebrows
- eczema
- xanthomata

Skin manifestations of hyperthyroidism
- pretibial myxoedema: erythematous, oedematous lesions above the lateral malleoli
- thyroid acropachy: clubbing
- scalp hair thinning
- increased sweating

Pruritus can occur in both hyper- and hypothyroidism

# THYROID STORM

Thyroid storm is a rare but life-threatening complication of thyrotoxicosis. It is typically seen in patients with established thyrotoxicosis and is rarely seen as the presenting feature. Iatrogenic thyroxine excess does not usually result in thyroid storm.

Precipitating events:
- thyroid or non-thyroidal surgery
- trauma
- infection
- acute iodine load e.g. CT contrast media

Clinical features include:

- fever > 38.5ºC
- tachycardia
- confusion and agitation
- nausea and vomiting
- hypertension
- heart failure
- abnormal liver function test - jaundice may be seen clinically

Management:

- symptomatic treatment e.g. paracetamol
- treatment of underlying precipitating event
- beta-blockers: typically IV propranolol
- anti-thyroid drugs: e.g. methimazole or propylthiouracil
- Lugol's iodine
- dexamethasone - e.g. 4mg IV qds - blocks the conversion of T4 to T3

# THYROID CANCER

Features of hyperthyroidism or hypothyroidism are not commonly seen in patients with thyroid malignancies as they rarely secrete thyroid hormones

**Main points**

| Type | Percentage | |
|---|---|---|
| Papillary | 70% | Often young females - excellent prognosis |
| Follicular | 20% | |
| Medullary | 5% | Cancer of parafollicular (C) cells, secrete calcitonin, part of MEN-2 |
| Anaplastic | 1% | Not responsive to treatment, can cause pressure symptoms |
| Lymphoma | Rare | Associated with Hashimoto's thyroiditis |

Management of papillary and follicular cancer

- total thyroidectomy
- followed by radioiodine (I-131) to kill residual cells
- yearly thyroglobulin levels to detect early recurrent disease

**Further information**

| Type | Notes |
|---|---|
| Papillary carcinoma | • Usually contain a mixture of papillary and colloidal filled follicles<br>• Histologically tumour has papillary projections and pale empty nuclei<br>• Seldom encapsulated<br>• Lymph node metastasis predominate<br>• Haematogenous metastasis rare |
| Follicular adenoma | • Usually present as a solitary thyroid nodule<br>• Malignancy can only be excluded on formal histological assessment |
| Follicular carcinoma | • May appear macroscopically encapsulated, microscopically capsular invasion is seen. Without this finding the lesion is a follicular adenoma.<br>• Vascular invasion predominates<br>• Multifocal disease raree |
| Medullary carcinoma | • C cells derived from neural crest and not thyroid tissue<br>• Serum calcitonin levels often raised<br>• Familial genetic disease accounts for up to 20% cases<br>• Both lymphatic and haematogenous metastasis are recognised, nodal disease is associated with a very poor prognosis. |
| Anaplastic carcinoma | • Most common in elderly females<br>• Local invasion is a common feature<br>• Treatment is by resection where possible, palliation may be achieved through isthmusectomy and radiotherapy. Chemotherapy is ineffective. |

# HYPOPARATHYROIDISM

Primary hypoparathyroidism
- decrease PTH secretion
- e.g. secondary to thyroid surgery*
- low calcium, high phosphate
- treated with alfacalcidol

The main symptoms of hypoparathyroidism are secondary to hypocalcaemia:
- tetany: muscle twitching, cramping and spasm
- perioral paraesthesia
- Trousseau's sign: carpal spasm if the brachial artery occluded by inflating the blood pressure cuff and maintaining pressure above systolic
- Chvostek's sign: tapping over parotid causes facial muscles to twitch
- if chronic: depression, cataracts
- ECG: prolonged QT interval

Pseudohypoparathyroidism
- target cells being insensitive to PTH
- due to abnormality in a G protein
- associated with low IQ, short stature, shortened 4th and 5th metacarpals
- low calcium, high phosphate, high PTH
- diagnosis is made by measuring urinary cAMP and phosphate levels following an infusion of PTH. In hypoparathyroidism this will cause an increase in both cAMP and phosphate levels. In pseudohypoparathyroidism type I neither cAMP nor phosphate levels are increased whilst in pseudohypoparathyroidism type II only cAMP rises.

Pseudopseudohypoparathyroidism
- similar phenotype to pseudohypoparathyroidism but normal biochemistry

*this may seem an oxymoron, but most medical textbooks classify hypoparathyroidism which is secondary to surgery as being 'primary hypoparathyroidism'

# PSEUDOHYPOPARATHYROIDISM

Pseudohypoparathyroidism is caused by target cell insensitivity to parathyroid hormone (PTH) due to a mutation in a G-protein. In type I pseudohypoparathyroidism
there is a complete receptor defect whereas in type II the cell receptor is intact.
Pseudohypoparathyroidism is typically inherited in an autosomal dominant fashion*

Bloods
- PTH: high

- calcium: low
- phosphate: high

Features
- short fourth and fifth metacarpals
- short stature
- cognitive impairment
- obesity
- round face

Investigation
- infusion of PTH followed by measurement of urinary phosphate and cAMP measurement - this can help differentiate between type I (neither phosphate or cAMP levels rise) and II (cAMP rises but phosphate levels do not change)

*it was previously thought to be an X-linked dominant condition

# PRIMARY HYPERPARATHYROIDISM

In exams, primary hyperparathyroidism is stereotypically seen in elderly females with an unquenchable thirst and an inappropriately normal or raised parathyroid hormone level. It is most commonly due to a solitary adenoma

Causes of primary hyperparathyroidism
- 80%: solitary adenoma
- 15%: hyperplasia
- 4%: multiple adenoma
- 1%: carcinoma

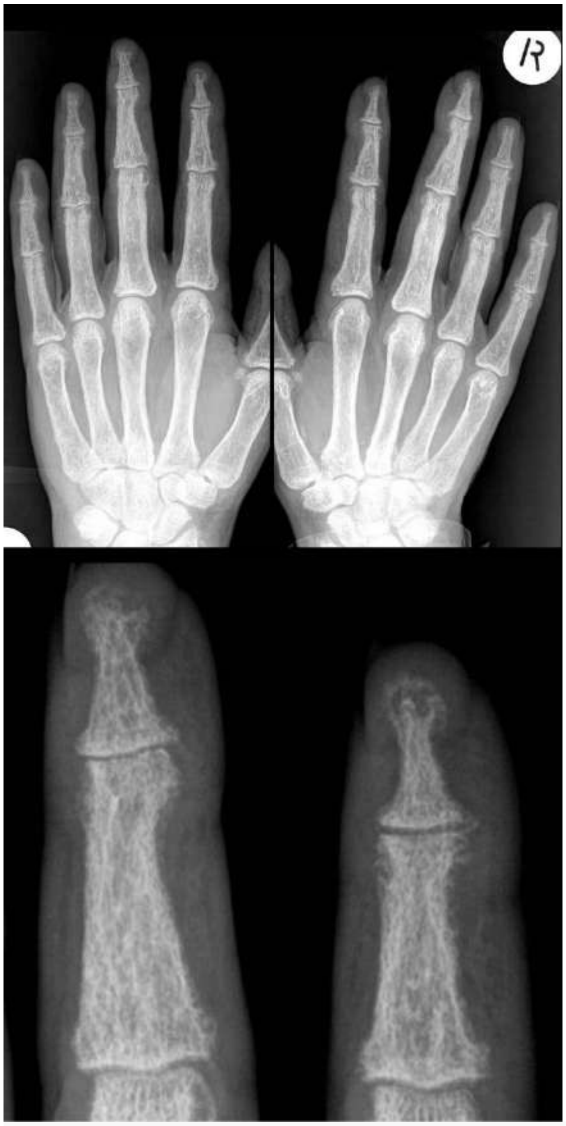
Features - 'bones, stones, abdominal groans and psychic moans'
- polydipsia, polyuria
- peptic ulceration/constipation/pancreatitis
- bone pain/fracture
- renal stones
- depression
- hypertension

Associations
- hypertension
- multiple endocrine neoplasia: MEN I and II

Investigations

- raised calcium, low phosphate
- PTH may be raised or (inappropriately, given the raised calcium) normal
- technetium-MIBI subtraction scan
- pepperpot skull is a characteristic X-ray finding of hyperparathyroidism

Treatment
- the definitive management is total parathyroidectomy
- conservative management may be offered if the calcium level is less than 0.25 mmol/L above the upper limit of normal AND the patient is > 50 years AND there is no evidence of end-organ damage
- calcimimetic agents such as cinacalcet are sometimes used in patients who are unsuitable for surgery



Bilateral hand radiographs in a middle-aged woman demonstrating generalised osteopenia, erosion of the terminal phalangeal tufts (acro-osteolysis) and subperiosteal resorption of bone particularly the radial aspects of the 2nd and 3rd middle phalanges. These changes are consistent with a diagnosis of hyperparathyroidism.

# CUSHING'S SYNDROME: CAUSES

It should be noted that exogenous causes of Cushing's syndrome (e.g. glucocorticoid therapy) are far more common than endogenous ones.

ACTH dependent causes
- Cushing's disease (80%): pituitary tumour secreting ACTH producing adrenal hyperplasia
- ectopic ACTH production (5-10%): e.g. small cell lung cancer

ACTH independent causes
- iatrogenic: steroids
- adrenal adenoma (5-10%)
- adrenal carcinoma (rare)
- Carney complex: syndrome including cardiac myxoma
- micronodular adrenal dysplasia (very rare)

Pseudo-Cushing's
- mimics Cushing's
- often due to alcohol excess or severe depression
- causes false positive dexamethasone suppression test or 24 hr urinary free cortisol
- insulin stress test may be used to differentiate

# CUSHING'S SYNDROME: INVESTIGATIONS

Investigations are divided into confirming Cushing's syndrome and then localising the lesion. A hypokalaemic metabolic alkalosis may be seen, along with impaired glucose tolerance. Ectopic ACTH secretion (e.g. secondary to small cell lung cancer) is characteristically associated with very low potassium levels. An insulin stress test is used to differentiate between true Cushing's and pseudo-Cushing's

**Tests to confirm Cushing's syndrome**
The two most commonly used tests are:
- overnight dexamethasone suppression test (most sensitive)
- 24 hr urinary free cortisol

**Localisation tests**
The first-line localisation is 9am and midnight plasma ACTH (and cortisol) levels. If ACTH is suppressed then a non-ACTH dependent cause is likely such as an adrenal adenoma

Both low- and high-dose dexamethasone suppression tests may be used to localise the pathology resulting in Cushing's syndrome. These tests may be interpreted as follows:

| Cortisol result | Interpretation |
|---|---|
| Not suppressed by low-dose dexamethasone | Cushing's syndrome not due to primary causes, i.e. likely secondary to corticosteroid therapy |
| Not suppressed by low-dose, but suppressed by high-dose dexamethasone | Cushing's disease |
| Not suppressed by low- or high-dose dexamethasone | Ectopic ACTH syndrome likely |

CRH stimulation

- if pituitary source then cortisol rises
- if ectopic/adrenal then no change in cortisol

Petrosal sinus sampling of ACTH may be needed to differentiate between pituitary and ectopic ACTH secretion

# ADDISON'S DISEASE

Autoimmune destruction of the adrenal glands is the commonest cause of primary hypoadrenalism in the UK, accounting for 80% of cases. This is termed Addison's disease and results in reduced cortisol and aldosterone being produced.

Features
- lethargy, weakness, anorexia, nausea & vomiting, weight loss, 'salt-craving'
- hyperpigmentation (especially palmar creases)*, vitiligo, loss of pubic hair in women, hypotension, hypoglycaemia
- hyponatraemia and hyperkalaemia may be seen
- crisis: collapse, shock, pyrexia

**Other causes of hypoadrenalism**

Primary causes
- tuberculosis
- metastases (e.g. bronchial carcinoma)
- meningococcal septicaemia (Waterhouse-Friderichsen syndrome)
- HIV
- antiphospholipid syndrome

Secondary causes
- pituitary disorders (e.g. tumours, irradiation, infiltration)

Exogenous glucocorticoid therapy

*Primary Addison's is associated with hyperpigmentation whereas secondary adrenal insufficiency is not

# ADDISON'S DISEASE: INVESTIGATIONS

In a patient with suspected Addison's disease the definite investigation is an ACTH stimulation test (short Synacthen test). Plasma cortisol is measured before and 30 minutes after giving Synacthen 250ug IM. Adrenal autoantibodies such as anti-21-hydroxylase may also be demonstrated.

If an ACTH stimulation test is not readily available (e.g. in primary care) then sending a 9 am serum cortisol can be useful:
- > 500 nmol/l makes Addison's very unlikely
- < 100 nmol/l is definitely abnormal
- 100-500 nmol/l should prompt a ACTH stimulation test to be performed

Associated electrolyte abnormalities are seen in around one-third of undiagnosed patients:
- hyperkalaemia
- hyponatraemia
- hypoglycaemia
- metabolic acidosis

# ADDISONIAN CRISIS

Causes
- sepsis or surgery causing an acute exacerbation of chronic insufficiency (Addison's, Hypopituitarism)
- adrenal haemorrhage eg Waterhouse-Friderichsen syndrome (fulminant meningococcemia)
- steroid withdrawal

Management
- hydrocortisone 100 mg im or iv
- 1 litre normal saline infused over 30-60 mins or with dextrose if hypoglycaemic
- continue hydrocortisone 6 hourly until the patient is stable. No fludrocortisone is required because high cortisol exerts weak mineralocorticoid action
- oral replacement may begin after 24 hours and be reduced to maintenance over 3-4 days

# AUTOIMMUNE POLYENDOCRINOPATHY SYNDROME

Addison's disease (autoimmune hypoadrenalism) is associated with other endocrine deficiencies in approximately 10% of patients. There are two distinct types of autoimmune polyendocrinopathy syndrome (APS), with type 2 (sometimes referred to as Schmidt's syndrome) being much more common.

APS type 2 has a polygenic inheritance and is linked to HLA DR3/DR4. Patients have Addison's disease plus either:
- type 1 diabetes mellitus
- autoimmune thyroid disease

APS type 1 is occasionally referred to as Multiple Endocrine Deficiency Autoimmune Candidiasis (MEDAC). It is a very rare autosomal recessive disorder caused by mutation of AIRE1 gene on chromosome 21

Features of APS type 1 (2 out of 3 needed)
- chronic mucocutaneous candidiasis (typically first feature as young child)
- Addison's disease

- primary hypoparathyroidism

Vitiligo can occur in both types

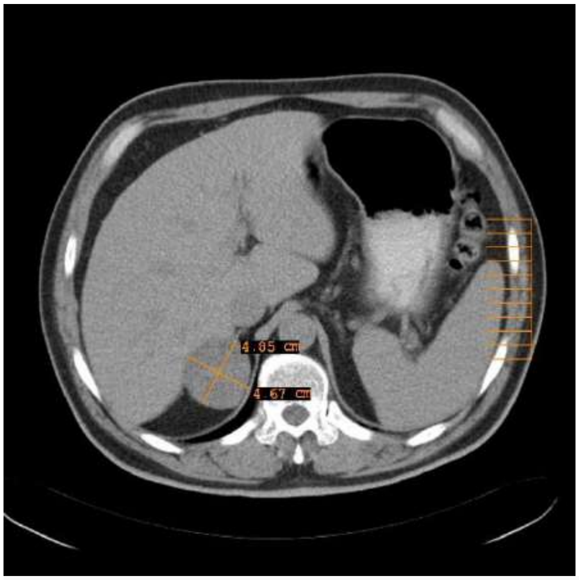
# PRIMARY HYPERALDOSTERONISM

Primary hyperaldosteronism was previously thought to be most commonly caused by an adrenal adenoma, termed Conn's syndrome. However, recent studies have shown that bilateral idiopathic adrenal hyperplasia is the cause in up to 70% of cases. Differentiating between the two is important as this determines treatment. Adrenal carcinoma is an extremely rare cause of primary hyperaldosteronism.

Features
- **hypertension**
- **hypokalaemia**
    a. e.g. muscle weakness
    b. this is a classical feature in exams but studies suggest this is seen in only 10-40% of patients
- alkalosis

Investigations
- the 2016 Endocrine Society recommend that a plasma **aldosterone/renin ratio is the first-line investigation** in suspected primary hyperaldosteronism
    - should show high aldosterone levels alongside low renin levels (negative feedback due to sodium retention from aldosterone)
- following this a high-resolution CT abdomen and adrenal vein sampling is used to differentiate between unilateral and bilateral sources of aldosterone excess
- Adrenal Venous Sampling (AVS) can be done to identify the gland secreting excess hormone in primary hyperaldosteronism

Management
- adrenal adenoma: surgery
- bilateral adrenocortical hyperplasia: aldosterone antagonist e.g. spironolactone



CT abdomen showing a right-sided adrenal adenoma in a patient who presented with hypertension and hypokalaemia. The adenoma can be seen 'next to' or 'below' the liver.

# PHAEOCHROMOCYTOMA

Phaeochromocytoma is a rare catecholamine secreting tumour. About 10% are familial and may be associated with MEN type II, neurofibromatosis and von Hippel-Lindau syndrome

Basics
- bilateral in 10%
- malignant in 10%
- extra-adrenal in 10% (most common site = organ of Zuckerkandl, adjacent to the bifurcation of the aorta)

Features are typically episodic
- hypertension (around 90% of cases, may be sustained)
- headaches
- palpitations
- sweating
- anxiety

Tests
- 24 hr urinary collection of metanephrines (sensitivity 97%*)
- this has replaced a 24 hr urinary collection of catecholamines (sensitivity 86%)

Surgery is the definitive management. The patient must first however be stabilized with medical management:
- alpha-blocker (e.g. phenoxybenzamine), given before a
- beta-blocker (e.g. propranolol)

*BMJ 2012; 344 doi: http://dx.doi.org/10.1136/bmj.e1042 (Published 20 February 2012)

# ACROMEGALY: FEATURES

In acromegaly there is excess growth hormone secondary to a pituitary adenoma in over 95% of cases. A minority of cases are caused by ectopic GHRH or GH production by tumours e.g. pancreatic.

Features
- coarse facial appearance, spade-like hands, increase in shoe size
- large tongue, prognathism, interdental spaces
- excessive sweating and oily skin: caused by sweat gland hypertrophy
- features of pituitary tumour: hypopituitarism, headaches, bitemporal hemianopia
- raised prolactin in 1/3 of cases → galactorrhoea
- 6% of patients have MEN-1

Complications
- hypertension
- diabetes (>10%)
- cardiomyopathy
- colorectal cancer

# ACROMEGALY: INVESTIGATIONS

Growth hormone (GH) levels vary during the day and are therefore not diagnostic.

**Serum IGF-1 levels** have now overtaken the oral glucose tolerance test (OGTT) with serial GH measurements as the first-line test. The OGTT test is recommended to confirm the diagnosis if IGF-1 levels are raised.

The Endocrine Society guidelines suggest the following:

*1.1 We recommend measurement of IGF-1 levels in patients with typical clinical manifestations of acromegaly, especially those with acral and facial features.*
...
*1.5 In patients with elevated or equivocal serum IGF-1 levels, we recommend confirmation of the diagnosis by finding lack of suppression of GH to < 1 µg/L following documented hyperglycemia during an oral glucose load.*

Serum IGF-1 may also be used to monitor disease

Oral glucose tolerance test
- in normal patients GH is suppressed to < 2 mu/L with hyperglycaemia
- in acromegaly there is no suppression of GH
- may also demonstrate impaired glucose tolerance which is associated with acromegaly

A pituitary MRI may demonstrate a pituitary tumour.

## ACROMEGALY: MANAGEMENT

Trans-sphenoidal surgery is the first-line treatment for acromegaly in the majority of patients

Dopamine agonists
- for example bromocriptine
- the first effective medical treatment for acromegaly, however now superseded by somatostatin analogues
- effective only in a minority of patients

Somatostatin analogue
- directly inhibits the release of growth hormone
- for example octreotide
- effective in 50-70% of patients
- may be used as an adjunct to surgery

Pegvisomant
- GH receptor antagonist - prevents dimerization of the GH receptor
- once daily s/c administration
- very effective - decreases IGF-1 levels in 90% of patients to normal
- doesn't reduce tumour volume therefore surgery still needed if mass effect

External irradiation is sometimes used for older patients or following failed surgical/medical treatment

# PROLACTIN AND GALACTORRHOEA

Prolactin is secreted by the anterior pituitary gland with release being controlled by a wide variety of physiological factors. Dopamine acts as the primary prolactin releasing inhibitory factor and hence dopamine agonists such as bromocriptine may be used to control galactorrhoea. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Features of excess prolactin

- men: impotence, loss of libido, galactorrhoea
- women: amenorrhoea, galactorrhoea

Causes of raised prolactin

- prolactinoma
- pregnancy
- oestrogens
- physiological: stress, exercise, sleep
- acromegaly: 1/3 of patients
- polycystic ovarian syndrome
- primary hypothyroidism (due to thyrotrophin releasing hormone (TRH) stimulating prolactin release)

Drug causes of raised prolactin

- metoclopramide, domperidone
- phenothiazines
- haloperidol
- very rare: SSRIs, opioids

# GYNAECOMASTIA

Gynaecomastia describes an abnormal amount of breast tissue in males and is usually caused by an increased oestrogen:androgen ratio. It is important to differentiate the causes of galactorrhoea (due to the actions of prolactin on breast tissue) from those of gynaecomastia

Causes of gynaecomastia
- physiological: normal in puberty
- syndromes with androgen deficiency: Kallman's, Klinefelter's
- testicular failure: e.g. mumps
- liver disease
- testicular cancer e.g. seminoma secreting hCG
- ectopic tumour secretion
- hyperthyroidism
- haemodialysis
- drugs: see below

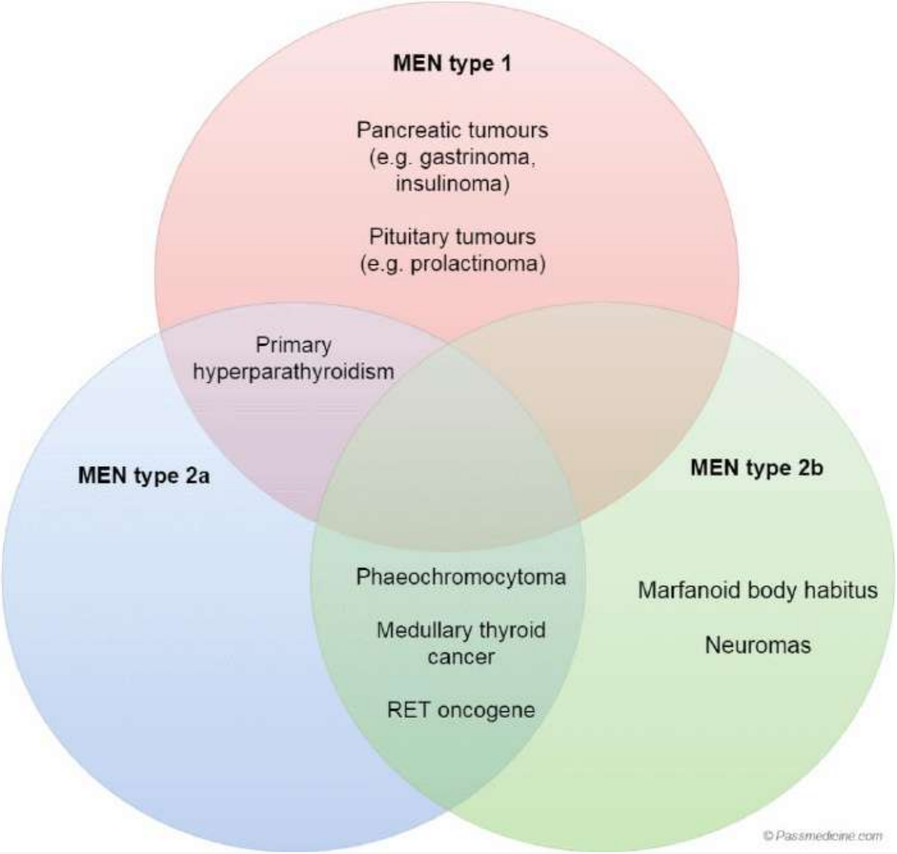
Drug causes of gynaecomastia
- spironolactone (most common drug cause)
- cimetidine
- digoxin
- cannabis
- finasteride
- GnRH agonists e.g. goserelin, buserelin
- oestrogens, anabolic steroids

Very rare drug causes of gynaecomastia
- tricyclics
- isoniazid
- calcium channel blockers
- heroin
- busulfan
- methyldopa

# MULTIPLE ENDOCRINE NEOPLASIA

The table below summarises the three main types of multiple endocrine neoplasia (MEN). MEN is inherited as an autosomal dominant disorder.

| MEN type I | MEN type IIa | MEN type IIb |
|---|---|---|
| 3 **P**'s<br>**P**arathyroid (95%): hyperparathyroidism due to parathyroid hyperplasia<br>**P**ituitary (70%)<br>**P**ancreas (50%): e.g. insulinoma, gastrinoma (leading to recurrent peptic ulceration)<br><br>Also: adrenal and thyroid | Medullary thyroid cancer (70%)<br><br>2 **P**'s<br>**P**arathyroid (60%)<br>**P**haeochromocytoma | Medullary thyroid cancer<br><br>1 **P**<br>**P**haeochromocytoma<br><br>Marfanoid body habitus<br>Neuromas |
| MEN1 gene<br><br>Most common presentation = hypercalcaemia | RET oncogene | RET oncogene |


MEN type 1
Pancreatic tumours (e.g. gastrinoma, insulinoma)
Pituitary tumours (e.g. prolactinoma)
Primary hyperparathyroidism
MEN type 2a
MEN type 2b
Phaeochromocytoma
Medullary thyroid cancer
RET oncogene
Marfanoid body habitus
Neuromas
© Passmedicine.com

Venn diagram showing the different types of MEN and their associated features

# PITUITARY ADENOMA

A pituitary adenoma is a benign tumour of the pituitary gland. They are common (10% of all people1) but in most cases will never be found (asymptomatic) or are found as an incidental finding. They account for around 10% of adult brain tumours2.

Pituitary adenomas can be classified according to:
- **size** (a microadenoma is <1cm and a macroadenoma is >1cm)
- **hormonal status** (a secretory/functioning adenoma produces and excess of a particular hormone and a non-secretory/functioning adenoma does not produce a hormone to excess)

Prolactinomas are the most common type and they produce an excess of prolactin. After prolactinomas, non-secreting adenomas are the next most common, then GH secreting and then ACTH secreting adenomas.

Pituitary adenomas typically cause symptoms by:
- excess of a hormone (e.g. Cushing's disease due to excess ACTH, acromegaly due to excess GH or amenorrhea and galactorrhea due to excess prolactin)
- depletion of a hormone(s) (due to compression of the normal functioning pituitary gland)
  - non-functioning tumours, therefore, present with generalised hypopituitarism
- stretching of the dura within/around pituitary fossa (causing headaches)
- compression of the optic chiasm (causing a bitemporal hemianopia due to crossing nasal fibers)

Alternatively, pituitary adenomas, particularly microadenomas, can be an incidental finding on neuroimaging and therefore called a 'pituitary incidentaloma'.

Investigation requires:
- a pituitary blood profile (including: GH, prolactin, ACTH, FH, LSH and TFTs)
- formal visual field testing
- MRI brain with contrast

Differential diagnoses include:
- pituitary hyperplasia
- craniopharyngioma
- meningioma
- brain metastases
- lymphoma
- hypophysitis
- vascular malformation (e.g. aneurysm)

Treatment may include a combination of:
- hormonal therapy (e.g. bromocriptine is the first line treatment for prolactinomas)
- surgery (e.g. transsphenoidal transnasal hypophysectomy)

  - e.g. if progression in size
- radiotherapy

# DISORDERS OF SEX DEVELOPMENT

The table below lists the most common disorders of sex development:

| Name | Karyotype | Notes |
|---|---|---|
| Androgen insensitivity syndrome | 46 XY | X-linked recessive condition. Defect in androgen receptor results in end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype. Rudimentary vagina and testes present but no uterus. Testosterone, oestrogen and LH levels are elevated |
| 5-α reductase deficiency | 46 XY | Autosomal recessive condition. Results in the inability of males to convert testosterone to dihydrotestosterone (DHT). Individuals have ambiguous genitalia in the newborn period. Hypospadias is common. Virilization at puberty. |
| Male pseudohermaphroditism | 46 XY | Individual has testes but external genitalia are female or ambiguous. may be secondary to androgen insensitivity syndrome |
| Female pseudohermaphroditism | 46 XX | Individual has ovaries but external genitalia are male (virilized) or ambiguous. May be secondary to congenital adrenal hyperplasia |
| True hermaphroditism | 46 XX or 47 XXY | Very rare, both ovarian and testicular tissue are present |

# ANDROGEN INSENSITIVITY SYNDROME

Androgen insensitivity syndrome is an X-linked recessive condition due to end-organ resistance to testosterone causing genotypically male children (46XY) to have a female phenotype. Complete androgen insensitivity syndrome is the new term for testicular feminisation syndrome

Features
- 'primary amennorhoea'
- undescended testes causing groin swellings
- breast development may occur as a result of conversion of testosterone to oestradiol

Diagnosis
- buccal smear or chromosomal analysis to reveal 46XY genotype

Management
- counselling - raise child as female
- bilateral orchidectomy (increased risk of testicular cancer due to undescended testes)
- oestrogen therapy

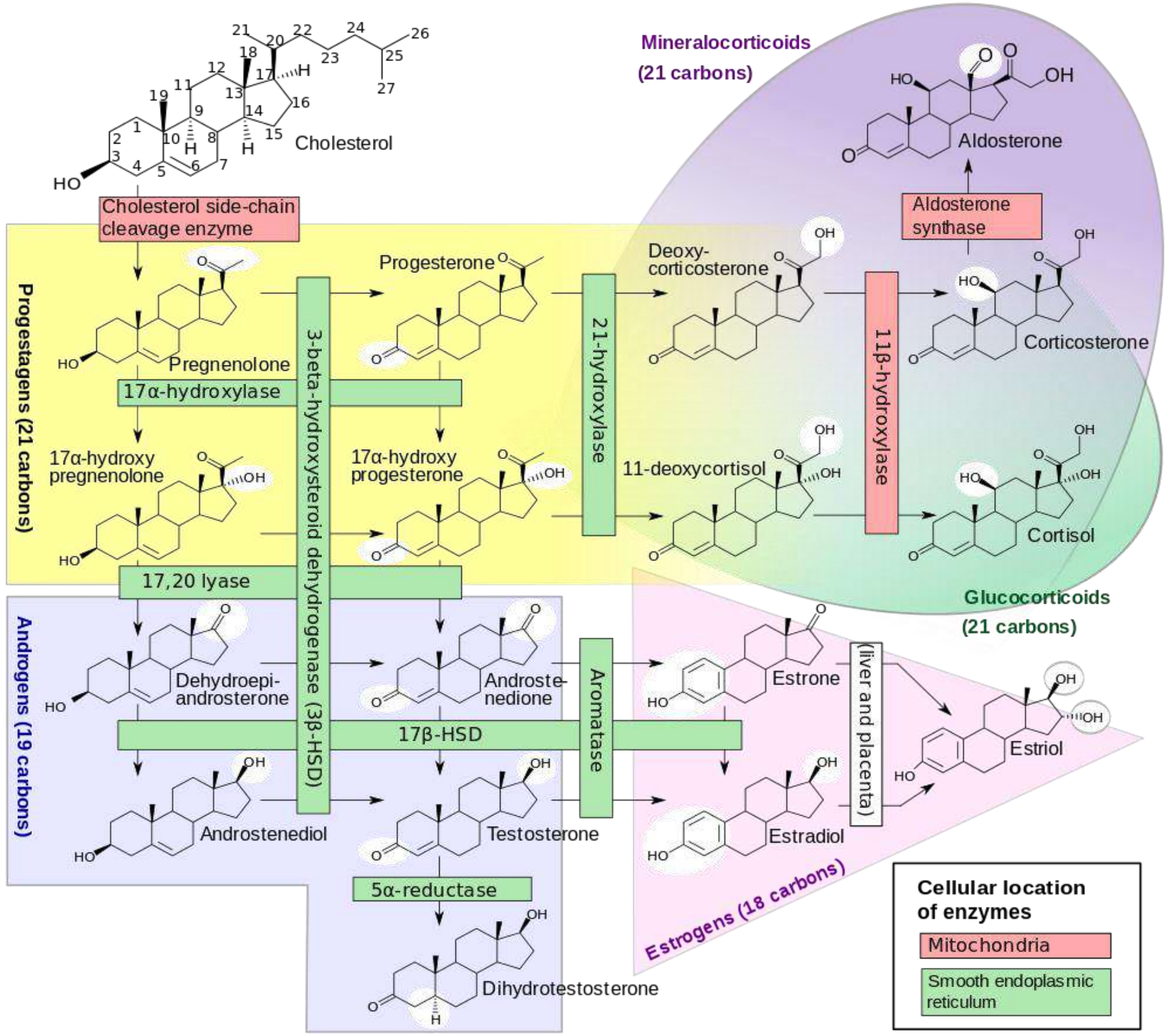
# CONGENITAL ADRENAL HYPERPLASIA

Overview

- group of autosomal recessive disorders
- affect adrenal steroid biosynthesis
- in response to resultant low cortisol levels the anterior pituitary secretes high levels of ACTH
- ACTH stimulates the production of adrenal androgens that may virilize a female infant

Cause

- 21-hydroxylase deficiency (90%)
- 11-beta hydroxylase deficiency (5%)
- 17-hydroxylase deficiency (very rare)


Cholesterol
Cholesterol side-chain cleavage enzyme
Progestagens (21 carbons)
Pregnenolone
17α-hydroxylase
17α-hydroxy pregnenolone
17,20 lyase
3-beta-hydroxysteroid dehydrogenase (3β-HSD)
Progesterone
17α-hydroxy progesterone
21-hydroxylase
Deoxy-corticosterone
11-deoxycortisol
11β-hydroxylase
Mineralocorticoids (21 carbons)
Aldosterone
Aldosterone synthase
Corticosterone
Cortisol
Glucocorticoids (21 carbons)
Androgens (19 carbons)
Dehydroepi-androsterone
Androste-nedione
17β-HSD
Androstenediol
Testosterone
5α-reductase
Dihydrotestosterone
Aromatase
Estrone
Estradiol
(liver and placenta)
Estriol
Estrogens (18 carbons)
Cellular location of enzymes
Mitochondria
Smooth endoplasmic reticulum

# KALLMANN'S SYNDROME

Kallmann's syndrome is a recognised cause of delayed puberty secondary to hypogonadotrophic hypogonadism. It is usually inherited as an X-linked recessive trait. Kallmann's syndrome is thought to be caused by failure of GnRH-secreting neurons to migrate to the hypothalamus.

The clue given in many questions is lack of smell (anosmia) in a boy with delayed puberty

Features
- 'delayed puberty'
- hypogonadism, cryptorchidism
- anosmia
- sex hormone levels are low
- LH, FSH levels are inappropriately low/normal
- patients are typically of normal or above average height

Cleft lip/palate and visual/hearing defects are also seen in some patients

# KLINEFELTER'S SYNDROME

Klinefelter's syndrome is associated with karyotype 47, XXY.

Features
- often taller than average
- lack of secondary sexual characteristics
- small, firm testes
- infertile
- gynaecomastia - increased incidence of breast cancer
- elevated gonadotrophin levels but low testosterone

Diagnosis is by karyotype (chromosomal analysis).

# POLYCYSTIC OVARIAN SYNDROME: FEATURES AND INVESTIGATION

Polycystic ovary syndrome (PCOS) is a complex condition of ovarian dysfunction thought to affect between 5-20% of women of reproductive age. The aetiology of PCOS is not fully understood. Both hyperinsulinaemia and high levels of luteinizing hormone are seen in PCOS and there appears to be some overlap with the metabolic syndrome.

Features
- subfertility and infertility
- menstrual disturbances: oligomenorrhea and amenorrhoea
- hirsutism, acne (due to hyperandrogenism)
- obesity
- acanthosis nigricans (due to insulin resistance)

Investigations
- pelvic ultrasound: multiple cysts on the ovaries
- FSH, LH, prolactin, TSH, and testosterone are useful investigations: raised LH:FSH ratio is a 'classical' feature but is no longer thought to be useful in diagnosis. Prolactin may be normal or mildly elevated. Testosterone may be normal or mildly elevated - however, if markedly raised consider other causes
- check for impaired glucose tolerance

# POLYCYSTIC OVARIAN SYNDROME: MANAGEMENT

Polycystic ovarian syndrome (PCOS) is a complex condition of ovarian dysfunction thought to affect between 5-20% of women of reproductive age. Management is complicated and problem based partly because the aetiology of PCOS is not fully understood. Both hyperinsulinaemia and high levels of luteinizing hormone are seen in PCOS and there appears to be some overlap with the metabolic syndrome.

General
- weight reduction if appropriate
- if a women requires contraception then a combined oral contraceptive (COC) pill may help regulate her cycle and induce a monthly bleed (see below)

Hirsutism and acne
- a COC pill may be used help manage hirsutism. Possible options include a third generation COC which has fewer androgenic effects or co-cyprindiol which has an anti-androgen action. Both of these types of COC may carry an increased risk of venous thromboembolism
- if doesn't respond to COC then topical eflornithine may be tried
- spironolactone, flutamide and finasteride may be used under specialist supervision

Infertility

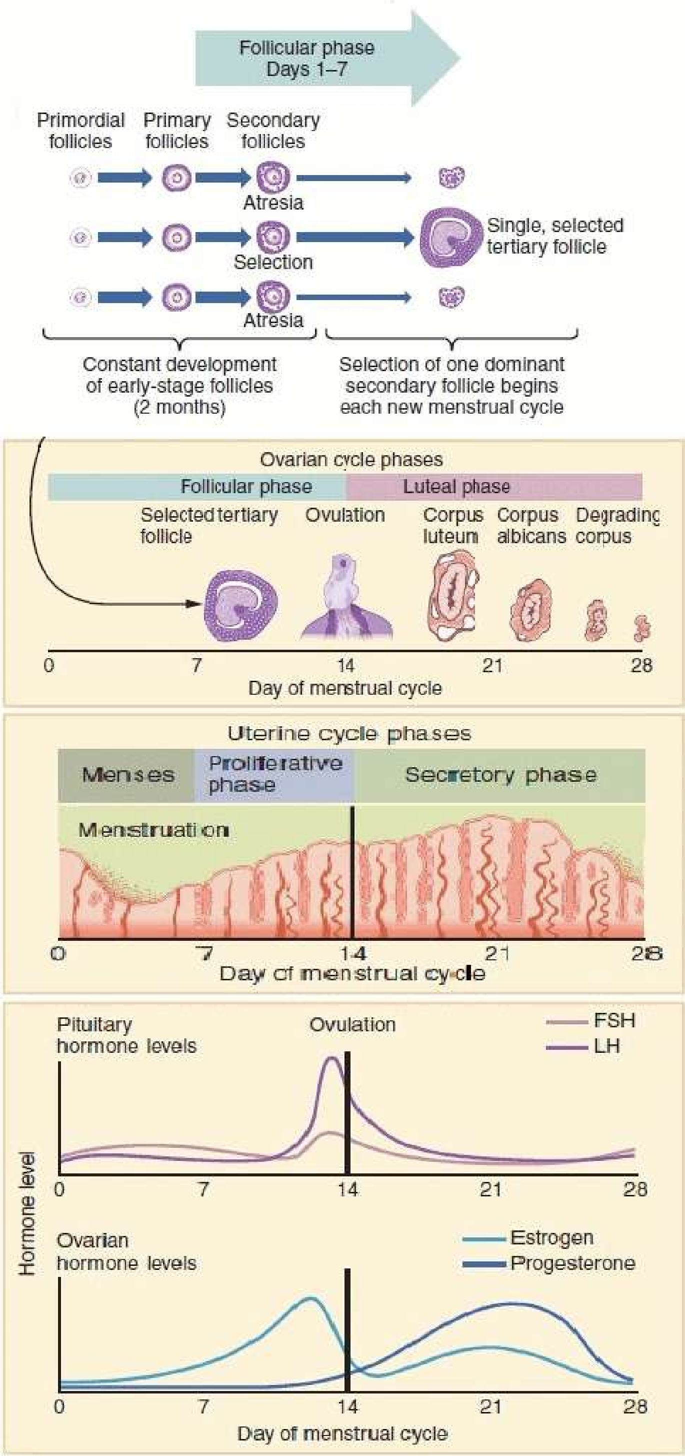
- weight reduction if appropriate
- the management of infertility in patients with PCOS should be supervised by a specialist. There is an ongoing debate as to whether metformin, clomifene or a combination should be used to stimulate ovulation
- a 2007 trial published in the New England Journal of Medicine suggested clomifene was the most effective treatment. There is a potential risk of multiple pregnancies with anti-oestrogen* therapies such as clomifene. The RCOG published an opinion paper in 2008 and concluded that on current evidence metformin is not a first line treatment of choice in the management of PCOS
- metformin is also used, either combined with clomifene or alone, particularly in patients who are obese
- gonadotrophins

*work by occupying hypothalamic oestrogen receptors without activating them. This interferes with the binding of oestradiol and thus prevents negative feedback inhibition of FSH secretion

# MENSTRUAL CYCLE

The menstrual cycle may be divided into the following phases:

| | Days |
|---|---|
| **Menstruation** | 1-4 |
| **Follicular phase (proliferative phase)** | 5-13 |
| **Ovulation** | 14 |
| **Luteal phase (secretory phase)** | 15-28 |


Follicular phase
Days 1–7
Primordial follicles
Primary follicles
Secondary follicles
Atresia
Selection
Atresia
Single, selected tertiary follicle
Constant development of early-stage follicles (2 months)
Selection of one dominant secondary follicle begins each new menstrual cycle
Ovarian cycle phases
Follicular phase
Luteal phase
Selected tertiary follicle
Ovulation
Corpus luteum
Corpus albicans
Degrading corpus
0
7
14
21
28
Day of menstrual cycle
Uterine cycle phases
Menses
Proliferative phase
Secretory phase
Menstruation
0
7
14
21
28
Day of menstrual cycle
Pituitary hormone levels
Ovulation
FSH
LH
0
7
14
21
28
Hormone level
Ovarian hormone levels
Estrogen
Progesterone
0
7
14
21
28
Day of menstrual cycle

Further details are given in the table below

| | Follicular phase (proliferative phase) | Luteal phase (secretory phase) |
|---|---|---|
| **Ovarian histology** | A number of follicles develop.<br>One follicle will become dominant around the mid-follicular phase | Corpus luteum |
| **Endometrial histology** | Proliferation of endometrium | Endometrium changes to secretory lining under influence of progesterone |
| **Hormones** | A rise in FSH results in the development of follicles which in turn secrete oestradiol<br>When the egg has matured, it secretes enough oestradiol to trigger the acute release of LH. This in turn leads to ovulation | Progesterone secreted by corpus luteum rises through the luteal phase.<br>If fertilisation does not occur the corpus luteum will degenerate and progesterone levels fall<br>Oestradiol levels also rise again during the luteal phase |
| **Cervical mucus** | Following menstruation the mucus is thick and forms a plug across the external os<br>Just prior to ovulation the mucus becomes clear, acellular, low viscosity. It also becomes 'stretchy' - a quality termed spinnbarkeit | Under the influence of progesterone it becomes thick, scant, and tacky |
| **Basal body temperature** | Falls prior to ovulation due to the influence of oestradiol | Rises following ovulation in response to higher progesterone levels |

# AMENORRHOEA

Amenorrhoea may be divided into primary (failure to start menses by the age of 16 years) or secondary (cessation of established, regular menstruation for 6 months or longer).

Causes of primary amenorrhoea
- Turner's syndrome
- testicular feminisation
- congenital adrenal hyperplasia
- congenital malformations of the genital tract

Secondary amenorrhoea is defined as when menstruation has previously occurred but has now stopped for at least 6 months.

Causes of secondary amenorrhoea (after excluding pregnancy)
- hypothalamic amenorrhoea (e.g. Stress, excessive exercise)
- polycystic ovarian syndrome (PCOS)
- hyperprolactinaemia
- premature ovarian failure
- thyrotoxicosis*
- Sheehan's syndrome
- Asherman's syndrome (intrauterine adhesions)

Initial investigations
- exclude pregnancy with urinary or serum bHCG
- gonadotrophins: low levels indicate a hypothalamic cause where as raised levels suggest an ovarian problem (e.g. Premature ovarian failure)
- prolactin
- androgen levels: raised levels may be seen in PCOS
- oestradiol
- thyroid function tests

*hypothyroidism may also cause amenorrhoea

# PREMATURE OVARIAN FAILURE

Premature ovarian failure is defined as the onset of menopausal symptoms and elevated gonadotrophin levels before the age of 40 years. It occurs in around 1 in 100 women.

Causes
- idiopathic - the most common cause
- chemotherapy

- autoimmune
- radiation

Features are similar to those of the normal climacteric but the actual presenting problem may differ
- climacteric symptoms: hot flushes, night sweats
- infertility
- secondary amenorrhoea
- raised FSH, LH levels

## HORMONE REPLACEMENT THERAPY: ADVERSE EFFECTS

Hormone replacement therapy (HRT) involves the use of a small dose of oestrogen (combined with a progestogen in women with a uterus) to help alleviate menopausal symptoms.

Side-effects
- nausea
- breast tenderness
- fluid retention and weight gain

Potential complications
- increased risk of breast cancer
  - increased by the addition of a progestogen
  - in the Women's Health Initiative (WHI) study there was a relative risk of 1.26 at 5 years of developing breast cancer
  - the increased risk relates to the duration of use
  - the risk of breast cancer begins to decline when HRT is stopped and by 5 years it reaches the same level as in women who have never taken HRT
- increased risk of endometrial cancer
  - oestrogen by itself should not be given as HRT to women with a womb
  - reduced by the addition of a progestogen but not eliminated completely
  - the BNF states that the additional risk is eliminated if a progestogen is given continuously
- increased risk of venous thromboembolism
  - increased by the addition of a progestogen
  - transdermal HRT does not appear to increase the risk of VTE
  - NICE state women requesting HRT who are at high risk for VTE should be referred to haematology before starting any treatment (even transdermal)
- increased risk of stroke
- increased risk of ischaemic heart disease if taken more than 10 years after menopause

# CERVICAL CANCER

Around 50% of cases of cervical cancer occur in women under the age of 45 years, with incidence rates for cervical cancer in the UK are highest in people aged 25-29 years, according to Cancer Research UK. It may be divided into:

- squamous cell cancer (80%)
- adenocarcinoma (20%)

Features

- may be detected during routine cervical cancer screening
- abnormal vaginal bleeding: postcoital, intermenstrual or postmenopausal bleeding
- vaginal discharge

Human papillomavirus (HPV), particularly serotypes 16,18 & 33 is by far the most important factor in the development of cervical cancer. Other risk factors include:

- smoking
- human immunodeficiency virus
- early first intercourse, many sexual partners
- high parity
- lower socioeconomic status
- combined oral contraceptive pill*

Mechanism of HPV causing cervical cancer

- HPV 16 & 18 produces the oncogenes E6 and E7 genes respectively
- E6 inhibits the p53 tumour suppressor gene
- E7 inhibits RB suppressor gene

*the strength of this association is sometimes debated but a large study published in the Lancet (2007 Nov 10;370(9599):1609-21) confirmed the link

# ENDOMETRIAL CANCER

Endometrial cancer is classically seen in post-menopausal women but around 25% of cases occur before the menopause. It usually carries a good prognosis due to early detection

The risk factors for endometrial cancer are as follows*:

- obesity
- nulliparity
- early menarche
- late menopause
- unopposed oestrogen. The addition of a progestogen to oestrogen reduces this risk (e.g. In HRT). The BNF states that the additional risk is eliminated if a progestogen is given continuously

- diabetes mellitus
- tamoxifen
- polycystic ovarian syndrome
- hereditary non-polyposis colorectal carcinoma

Features
- postmenopausal bleeding is the classic symptom
- premenopausal women may have a change intermenstrual bleeding
- pain and discharge are unusual features

Investigation
- women >= 55 years who present with postmenopausal bleeding should be referred using the suspected cancer pathway
- first-line investigation is trans-vaginal ultrasound - a normal endometrial thickness (< 4 mm) has a high negative predictive value
- hysteroscopy with endometrial biopsy

Management
- localised disease is treated with total abdominal hysterectomy with bilateral salpingo-oophorectomy. Patients with high-risk disease may have post-operative radiotherapy
- progestogen therapy is sometimes used in frail elderly women not consider suitable for surgery

*the combined oral contraceptive pill and smoking are protective

# OVARIAN CANCER

Ovarian cancer is the fifth most common malignancy in females. The peak age of incidence is 60 years and it generally carries a poor prognosis due to late diagnosis.

Pathophysiology
- around 90% of ovarian cancers are epithelial in origin, with 70-80% of cases being due to serous carcinomas
- interestingly, it is now increasingly recognised that the distal end of the fallopian tube is often the site of origin of many 'ovarian' cancers

Risk factors
- family history: mutations of the BRCA1 or the BRCA2 gene
- many ovulations*: early menarche, late menopause, nulliparity

Clinical features are notoriously vague
- abdominal distension and bloating
- abdominal and pelvic pain

- urinary symptoms e.g. Urgency
- early satiety
- diarrhoea

Investigations

- CA125
  - NICE recommends a CA125 test is done initially. Endometriosis, menstruation, benign ovarian cysts and other conditions may also raise the CA125 level
  - if the CA125 is raised (35 IU/mL or greater) then an urgent ultrasound scan of the abdomen and pelvis should be ordered
  - a CA125 should not be used for screening for ovarian cancer in asymptomatic women
- ultrasound

Diagnosis is difficult and usually involves diagnostic laparotomy

Management

- usually a combination of surgery and platinum-based chemotherapy

Prognosis

- 80% of women have advanced disease at presentation
- the all stage 5-year survival is 46%

*It is traditionally taught that infertility treatment increases the risk of ovarian cancer, as it increases the number of ovulations. Recent evidence however suggests that there is not a significant link. The combined oral contraceptive pill reduces the risk (fewer ovulations) as does having many pregnancies.

# BARTTER'S SYNDROME

Bartter's syndrome is an inherited cause (usually autosomal recessive) of severe hypokalaemia due to defective chloride absorption at the Na+ K+ 2Cl- cotransporter (NKCC2) in the ascending loop of Henle. It should be noted that it is associated with normotension (unlike other endocrine causes of hypokalaemia such as Conn's, Cushing's and Liddle's syndrome which are associated with hypertension).

Loop diuretics work by inhibiting NKCC2 - think of Bartter's syndrome as like taking large doses of furosemide

Features
usually presents in childhood, e.g. Failure to thrive
- polyuria, polydipsia
- hypokalaemia
- normotension
- weakness

# GITELMAN'S SYNDROME

Gitelman's syndrome is due to a defect in the thiazide-sensitive Na+ Cl- transporter in the distal convoluted tubule.

Features
- normotension
- hypokalaemia
- hypocalciuria
- hypomagnesaemia
- metabolic alkalosis

# LIDDLE'S SYNDROME

Liddle's syndrome is a rare autosomal dominant condition that causes hypertension and hypokalaemic alkalosis. It is thought to be caused by disordered sodium channels in the distal tubules leading to increased reabsorption of sodium.

Treatment is with either amiloride or triamterene

# PENDRED'S SYNDROME

Pendred is an autosomal recessive genetic disorder that is characterised by bilateral sensorineural deafness, with mild hypothyroidism and a goitre. The patients tend to present with progressive hearing loss and delay in academic progression. Often head trauma tends to make the sensorineural deafness worse, leading to patients having to avoid contact sports.

In Pendred syndrome there is a defect in the organification of iodine, leading to dyshormonogenesis. However thyroid symptoms in Pendred syndrome are often mild and patients are often clinically euthyroid, presenting only with a goitre. Thyroid function tests are also often normal, requiring the perchlorate discharge test to aid diagnosis.

The syndrome can be diagnosed via genetic testing (Pendred syndrome (PDS) gene, chromosome 7), audiometry and MRI imaging to look for characteristic one and a half turns in the cochlea, compared to the normal two and a half turns.

Treatment is with thyroid hormone replacement and cochlear implants.

# INSULINOMA

An insulinoma is a neuroendocrine tumour deriving mainly from pancreatic Islets of Langerhans cells

Basics

- most common pancreatic endocrine tumour
- 10% malignant, 10% multiple
- of patients with multiple tumours, 50% have MEN-1

Features

- of hypoglycaemia: typically early in morning or just before meal, e.g. diplopia, weakness etc
- rapid weight gain may be seen
- high insulin, raised proinsulin:insulin ratio
- high C-peptide

Diagnosis

- supervised, prolonged fasting (up to 72 hours)
- CT pancreas

Management

- surgery
- diazoxide and somatostatin if patients are not candidates for surgery

# NEUROBLASTOMA

Neuroblastoma is one of the top five causes of cancer in children, accounting for around 7-8% of childhood malignancies. The tumour arises from neural crest tissue of the adrenal medulla (the most common site) and sympathetic nervous system.

Median age of onset is around 20 months

Features
- abdominal mass
- pallor, weight loss
- bone pain, limp
- hepatomegaly
- paraplegia
- proptosis

Investigation
- raised urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA) levels
- calcification may be seen on abdominal x-ray
- biopsy

# CORTICOSTEROIDS AND THEIR SIDE EFFECTS

Corticosteroids are amongst the most commonly prescribed therapies in clinical practice. They are used both systemically (oral or intravenous) or locally (skin creams, inhalers, eye drops, intra-articular). They augment and in some cases replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

| Minimal glucocorticoid activity, very high mineralocorticoid activity, | Glucocorticoid activity, high mineralocorticoid activity, | Predominant glucocorticoid activity, low mineralocorticoid activity | Very high glucocorticoid activity, minimal mineralocorticoid activity |
|---|---|---|---|
| Fludrocortisone | Hydrocortisone | Prednisolone | Dexamethasone<br>Betmethasone |

**Side-effects**

The side-effects of corticosteroids are numerous and represent the single greatest limitation on their usage. Side-effects are more common with systemic and prolonged therapy.

Glucocorticoid side-effects

- endocrine: impaired glucose regulation, increased appetite/weight gain, hirsutism, hyperlipidaemia
- Cushing's syndrome: moon face, buffalo hump, striae
- musculoskeletal: osteoporosis, proximal myopathy, avascular necrosis of the femoral head
- immunosuppression: increased susceptibility to severe infection, reactivation of tuberculosis
- psychiatric: insomnia, mania, depression, psychosis
- gastrointestinal: peptic ulceration, acute pancreatitis
- ophthalmic: glaucoma, cataracts
- suppression of growth in children
- intracranial hypertension
- neutrophilia

Mineralocorticoid side-effects

- fluid retention
- hypertension

Selected points on the use of corticosteroids:

- patients on long-term steroids should have their doses doubled during intercurrent illness
- the BNF suggests gradual withdrawal of systemic corticosteroids if patients have: received more than 40mg prednisolone daily for more than one week, received more than 3 weeks treatment or recently received repeated courses

# DYNAMIC PITUITARY FUNCTION TESTS

A dynamic pituitary function test is used to assess patients with suspected primary pituitary dysfunction

Insulin, TRH and LHRH are given to the patient following which the serum glucose, cortisol, growth hormone, TSH, LH and FSH levels are recorded at regular intervals. Prolactin levels are also sometimes measured*

A normal dynamic pituitary function test has the following characteristics:

- GH level rises > 20mu/l
- cortisol level rises > 550 mmol/l
- TSH level rises by > 2 mu/l from baseline level
- LH and FSH should double

*dopamine antagonist tests using metoclopramide may also be used in the investigation of hyperprolactinaemia. A normal response is at least a twofold rise in prolactin. A blunted prolactin response suggests a prolactinoma

# WATER DEPRIVATION TEST

Method

- prevent patient drinking water
- ask patient to empty bladder
- hourly urine and plasma osmolalities

| | Starting plasma osm. | Final urine osm. | Urine osm. post-DDAVP |
|---|---|---|---|
| **Normal** | Normal | > 600 | > 600 |
| **Psychogenic polydipsia** | Low | > 400 | > 400 |
| **Cranial DI** | High | < 300 | > 600 |
| **Nephrogenic DI** | High | < 300 | < 300 |

# INSULIN STRESS TEST

Basics

- used in investigation of hypopituitarism
- IV insulin given, GH and cortisol levels measured
- with normal pituitary function GH and cortisol should rise

Contraindications

- epilepsy
- ischaemic heart disease
- adrenal insufficiency

# HYPERCALCAEMIA: CAUSES

Two conditions account for 90% of cases of hypercalcaemia:
1. Primary hyperparathyroidism: commonest cause in non-hospitalised patients
2. Malignancy: the commonest cause in hospitalised patients. This may be due to number of processes, including; bone metastases, myeloma, PTHrP from squamous cell lung cancer

Other causes include

- sarcoidosis*
- vitamin D intoxication
- acromegaly
- thyrotoxicosis
- Milk-alkali syndrome
- drugs: thiazides, calcium containing antacids
- dehydration
- Addison's disease
- Paget's disease of the bone**

*other causes of granulomas may lead to hypercalcaemia e.g. Tuberculosis and histoplasmosis

**usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

# URINARY INCONTINENCE

Urinary incontinence (UI) is a common problem, affecting around 4-5% of the population. It is more common in elderly females.

Risk factors
- advancing age
- previous pregnancy and childbirth
- high body mass index
- hysterectomy
- family history

Classification
- overactive bladder (OAB)/urge incontinence: due to detrusor overactivity
- stress incontinence: leaking small amounts when coughing or laughing
- mixed incontinence: both urge and stress
- overflow incontinence: due to bladder outlet obstruction, e.g. due to prostate enlargement

Initial investigation
- bladder diaries should be completed for a minimum of 3 days
- vaginal examination to exclude pelvic organ prolapse and ability to initiate voluntary contraction of pelvic floor muscles ('Kegel' exercises)
- urine dipstick and culture
- urodynamic studies

Management depends on whether urge or stress UI is the predominant picture. If urge incontinence is predominant:
- bladder retraining (lasts for a minimum of 6 weeks, the idea is to gradually increase the intervals between voiding)
- bladder stabilising drugs: antimuscarinics are first-line. NICE recommend oxybutynin (immediate release), tolterodine (immediate release) or darifenacin (once daily preparation). Immediate release oxybutynin should, however, be avoided in 'frail older women'
- mirabegron (a beta-3 agonist) may be useful if there is concern about anticholinergic side-effects in frail elderly patients

If stress incontinence is predominant:
- pelvic floor muscle training: NICE recommend at least 8 contractions performed 3 times per day for a minimum of 3 months
- surgical procedures: e.g. retropubic mid-urethral tape procedures

# PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease (PID) is a term used to describe infection and inflammation of the female pelvic organs including the uterus, fallopian tubes, ovaries and the surrounding peritoneum. It is usually the result of ascending infection from the endocervix.

Causative organisms

- Chlamydia trachomatis

+ the most common cause

- Neisseria gonorrhoeae
- Mycoplasma genitalium
- Mycoplasma hominis

Features

- lower abdominal pain
- fever
- deep dyspareunia
- dysuria and menstrual irregularities may occur
- vaginal or cervical discharge
- cervical excitation

Investigation

- a pregnancy test should be done to exclude an ectopic pregnancy
- high vaginal swab
- these are often negative
- screen for Chlamydia and Gonorrhoea

Management

- due to the difficulty in making an accurate diagnosis, and the potential complications of untreated PID, consensus guidelines recommend having a low threshold for treatment
- oral ofloxacin + oral metronidazole or intramuscular ceftriaxone + oral doxycycline + oral metronidazole
- RCOG guidelines suggest that in mild cases of PID intrauterine contraceptive devices may be left in. The more recent BASHH guidelines suggest that the evidence is limited but that ' Removal of the IUD should be considered and may be associated with better short term clinical outcomes'

Complications

- perihepatitis (Fitz-Hugh Curtis Syndrome)
  - occurs in around 10% of cases
  - it is characterised by right upper quadrant pain and may be confused with cholecystitis
- infertility - the risk may be as high as 10-20% after a single episode
- chronic pelvic pain
- ectopic pregnancy

# PASSMEDICINE NOTES NEUROLOGY

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# APHASIA

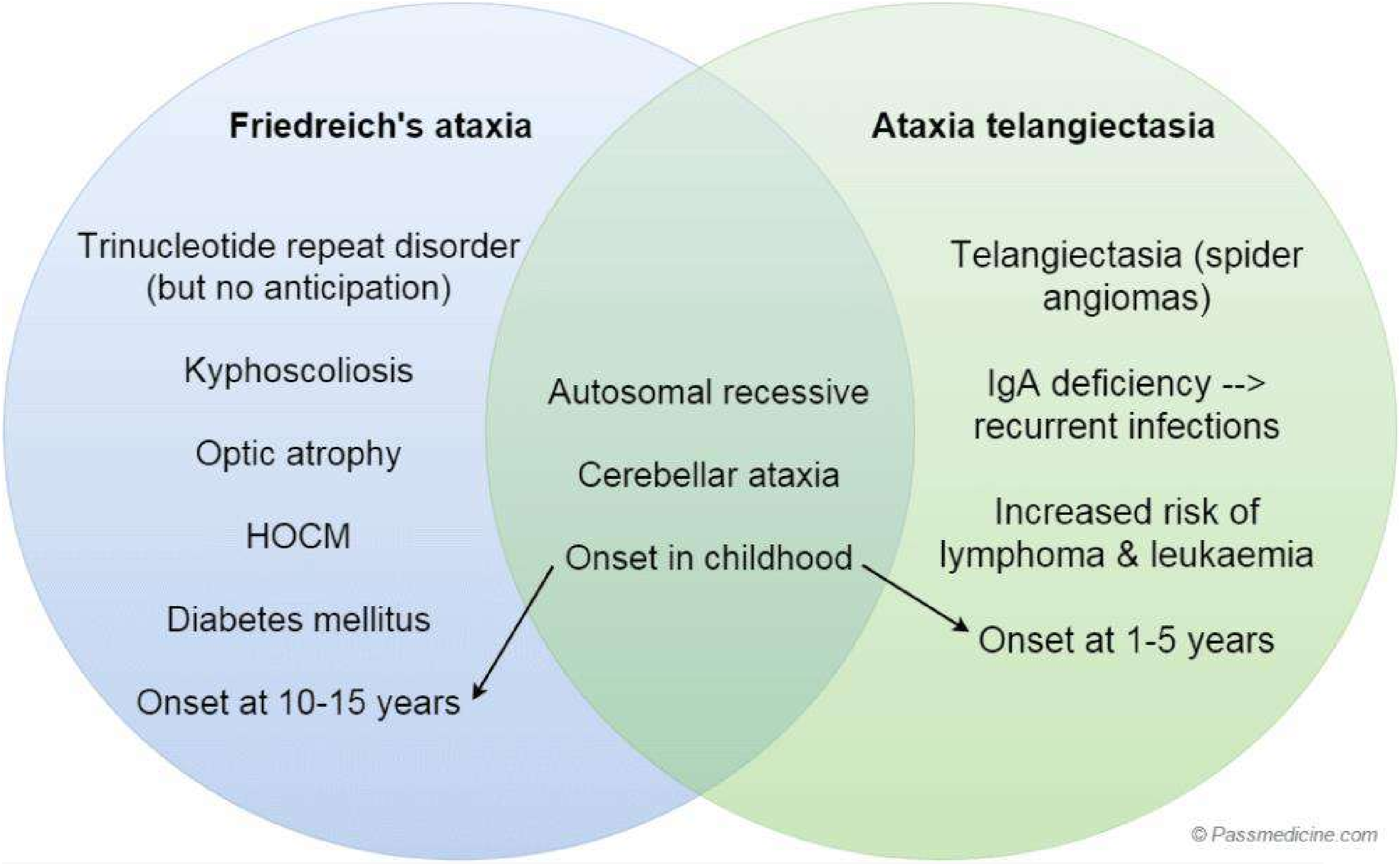
The table below lists the major types of aphasia. Remember that dysarthria is different and refers to a motor speech disorder.

| Type of aphasia | Notes |
|---|---|
| Wernicke's (receptive) aphasia | Due to a lesion of the superior temporal gyrus. It is typically supplied by the inferior division of the left MCA<br>This area 'forms' the speech before 'sending it' to Broca's area. Lesions result in sentences that make no sense, word substitution and neologisms but speech remains fluent<br>Comprehension is impaired |
| Broca's (expressive) aphasia | Due to a lesion of the inferior frontal gyrus. It is typically supplied by the superior division of the left MCA<br>Speech is non-fluent, laboured, and halting<br>Comprehension is normal |
| Conduction aphasia | Classically due to a stroke affecting the arcuate fasiculus - the connection between Wernicke's and Broca's area<br>Speech is fluent but repetition is poor. Aware of the errors they are making<br>Comprehension is normal |
| Global aphasia | Large lesion affecting all 3 of the above areas resulting in severe expressive and receptive aphasia |

# ATAXIA TELANGIECTASIA

Ataxia telangiectasia is an autosomal recessive disorder caused by a defect in the ATM gene which encodes for DNA repair enzymes. It is one of the inherited combined immunodeficiency disorders. It typically presents in early childhood with abnormal movements.

Features
- cerebellar ataxia
- telangiectasia (spider angiomas)
- IgA deficiency resulting in recurrent chest infections
- 10% risk of developing malignancy, lymphoma or leukaemia, but also non-lymphoid tumours


Friedreich's ataxia
Ataxia telangiectasia
Trinucleotide repeat disorder (but no anticipation)
Kyphoscoliosis
Optic atrophy
HOCM
Diabetes mellitus
Onset at 10-15 years
Autosomal recessive
Cerebellar ataxia
Onset in childhood
Telangiectasia (spider angiomas)
IgA deficiency --> recurrent infections
Increased risk of lymphoma & leukaemia
Onset at 1-5 years
© Passmedicine.com

Comparison of Friedreich's ataxia and ataxia telangiectasia. Note in particular how ataxia telangiectasia tends to present much earlier, often at the age of 1-2 years

# FRIEDREICH'S ATAXIA

Friedreich's ataxia is the most common of the early-onset hereditary ataxias. It is an autosomal recessive, trinucleotide repeat disorder characterised by a GAA repeat in the X25 gene on chromosome 9 (frataxin). Friedreich's ataxia is unusual amongst trinucleotide repeat disorders in not demonstrating the phenomenon of anticipation.

The typical age of onset is 10-15 years old. Gait ataxia and kyphoscoliosis are the most common presenting features.

Neurological features
- absent ankle jerks/extensor plantars
- cerebellar ataxia
- optic atrophy
- spinocerebellar tract degeneration

Other features
- hypertrophic obstructive cardiomyopathy (90%, most common cause of death)
- diabetes mellitus (10-20%)
- high-arched palate

# THIRD NERVE PALSY

Features

- eye is deviated 'down and out'
- ptosis
- pupil may be dilated (sometimes called a 'surgical' third nerve palsy)

Causes

- diabetes mellitus
- vasculitis e.g. temporal arteritis, SLE
- false localizing sign* due to uncal herniation through tentorium if raised ICP
- posterior communicating artery aneurysm
  - pupil dilated
  - often associated pain
- cavernous sinus thrombosis
- Weber's syndrome: ipsilateral third nerve palsy with contralateral hemiplegia -caused by midbrain strokes
- other possible causes: amyloid, multiple sclerosis

*this term is usually associated with sixth nerve palsies but it may be used for a variety of neurological presentations

# FOURTH NERVE PALSY

Overview

- supplies superior oblique (depresses eye, moves inward)

Features

- vertical diplopia
- classically noticed when reading a book or going downstairs
- subjective tilting of objects (torsional diplopia)
- the patient may develop a head tilt, which they may or may not be aware of
- when looking straight ahead, the affected eye appears to deviate upwards and is rotated outwards

# TRIGEMINAL NEURALGIA

Trigeminal neuralgia is a pain syndrome characterised by severe unilateral pain. The vast majority of cases are idiopathic but compression of the trigeminal roots by tumours or vascular problems may occur.

The International Headache Society defines trigeminal neuralgia as:
- a unilateral disorder characterised by brief electric shock-like pains, abrupt in onset and termination, limited to one or more divisions of the trigeminal nerve
- the pain is commonly evoked by light touch, including washing, shaving, smoking, talking, and brushing the teeth (trigger factors), and frequently occurs spontaneously
- small areas in the nasolabial fold or chin may be particularly susceptible to the precipitation of pain (trigger areas)
- the pains usually remit for variable periods

NICE Clinical Knowledge Summaries list the following as red flag symptoms and signs suggesting a serious underlying cause:
- Sensory changes
- Deafness or other ear problems
- History of skin or oral lesions that could spread perineurally
- Pain only in the ophthalmic division of the trigeminal nerve (eye socket, forehead, and nose), or bilaterally
- Optic neuritis
- A family history of multiple sclerosis
- Age of onset before 40 years

Management
- carbamazepine is first-line
- failure to respond to treatment or atypical features (e.g. < 50 years old) should prompt referral to neurology

# VISUAL FIELD DEFECTS

The main points for the exam are:
- left homonymous hemianopia means visual field defect to the left, i.e. Lesion of right optic tract
- homonymous quadrantanopias: PITS (Parietal-Inferior, Temporal-Superior)
- incongruous defects = optic tract lesion; congruous defects = optic radiation lesion or occipital cortex

A congruous defect simply means complete or symmetrical visual field loss and conversely an incongruous defect is incomplete or asymmetric. Please see the link for an excellent diagram.

Homonymous hemianopia

- incongruous defects: lesion of optic tract
- congruous defects: lesion of optic radiation or occipital cortex
- macula sparing: lesion of occipital cortex

Homonymous quadrantanopias*

- superior: lesion of temporal lobe
- inferior: lesion of parietal lobe
- mnemonic = PITS (Parietal-Inferior, Temporal-Superior)

Bitemporal hemianopia

- lesion of optic chiasm
- upper quadrant defect > lower quadrant defect = inferior chiasmal compression, commonly a pituitary tumour
- lower quadrant defect > upper quadrant defect = superior chiasmal compression, commonly a craniopharyngioma

*this is very much the 'exam answer'. Actual studies suggest that the majority of quadrantanopias are caused by occipital lobe lesions. Please see the link for more details.

# MIOSIS

Causes of miosis (small pupil)

- Horner's syndrome
- Argyll-Robertson pupil
- senile miosis
- pontine haemorrhage
- congenital

Drugs causes

- opiates
- parasympathomimetics: pilocarpine
- organophosphate toxicity

# FACIAL NERVE PALSY

The facial nerve is the main nerve supplying the structures of the second embryonic branchial arch. It is predominantly an efferent nerve to the muscles of facial expression, digastric muscle and also to many glandular structures. It contains a few afferent fibres which originate in the cells of its genicular ganglion and are concerned with taste.

Supply - 'face, ear, taste, tear'

- face: muscles of facial expression
- ear: nerve to stapedius
- taste: supplies anterior two-thirds of tongue
- tear: parasympathetic fibres to lacrimal glands, also salivary glands

Causes of bilateral facial nerve palsy

- sarcoidosis
- Guillain-Barre syndrome
- Lyme disease
- bilateral acoustic neuromas (as in neurofibromatosis type 2)
- as Bell's palsy is relatively common it accounts for up to 25% of cases f bilateral palsy, but this represents only 1% of total Bell's palsy cases

Causes of unilateral facial nerve palsy - as above plus

| **Lower motor neuron** | **Upper motor neuron** |
|---|---|
| • **Bell's palsy**<br>• **Ramsay-Hunt syndrome (due to herpes zoster)**<br>• **acoustic neuroma**<br>• **parotid tumours**<br>• **HIV**<br>• **multiple sclerosis***<br>• **diabetes mellitus** | • **stroke** |

LMN vs. UMN

- upper motor neuron lesion 'spares' upper face i.e. forehead
- lower motor neuron lesion affects all facial muscles

*may also cause an UMN palsy

**Path**

Subarachnoid path

- Origin: motor- pons, sensory- nervus intermedius
- Pass through the petrous temporal bone into the internal auditory meatus with the vestibulocochlear nerve. Here they combine to become the facial nerve.

Facial canal path

The canal passes superior to the vestibule of the inner ear

At the medial aspect of the middle ear, it becomes wider and contains the geniculate ganglion.
- 3 branches:
1. greater petrosal nerve
2. nerve to stapedius
3. chorda tympani

Stylomastoid foramen
- Passes through the stylomastoid foramen (tympanic cavity anterior and mastoid antrum posteriorly)
- Posterior auricular nerve and branch to posterior belly of digastric and stylohyoid muscle

# BELL'S PALSY

Bell's palsy may be defined as an acute, unilateral, idiopathic, facial nerve paralysis. The aetiology is unknown although the role of the herpes simplex virus has been investigated previously. The peak incidence is 20-40 years and the condition is more common in pregnant women.

Features
- lower motor neuron facial nerve palsy - forehead affected*
- patients may also notice post-auricular pain (may precede paralysis), altered taste, dry eyes, hyperacusis

Management
- in the past a variety of treatment options have been proposed including no treatment, prednisolone only and a combination of aciclovir and prednisolone
- following a National Institute for Health randomised controlled trial it is now recommended that prednisolone 1mg/kg for 10 days should be prescribed for patients within 72 hours of onset of Bell's palsy. Adding in aciclovir gives no additional benefit
- eye care is important - prescription of artificial tears and eye lubricants should be considered

Prognosis
- if untreated around 15% of patients have permanent moderate to severe weakness

*upper motor neuron lesion 'spares' upper face

# RAMSAY HUNT SYNDROME

Ramsay Hunt syndrome (herpes zoster oticus) is caused by the reactivation of the varicella zoster virus in the geniculate ganglion of the seventh cranial nerve.

Features

- auricular pain is often the first feature
- facial nerve palsy
- vesicular rash around the ear
- other features include vertigo and tinnitus

Management

- oral aciclovir and corticosteroids are usually given

# OTITIS EXTERNA

Otitis externa is a common reason for primary care attendance in the UK.

Causes of otitis externa include:
- infection: bacterial (Staphylococcus aureus, Pseudomonas aeruginosa) or fungal
- seborrhoeic dermatitis
- contact dermatitis (allergic and irritant)

Features
- ear pain, itch, discharge
- otoscopy: red, swollen, or eczematous canal

The recommended initial management of otitis externa is:
- topical antibiotic or a combined topical antibiotic with a steroid
- if the tympanic membrane is perforated aminoglycosides are traditionally not used*
- if there is canal debris then consider removal
- if the canal is extensively swollen then an ear wick is sometimes inserted

Second-line options include
- consider contact dermatitis secondary to neomycin
- oral antibiotics (flucloxacillin) if the infection is spreading
- taking a swab inside the ear canal
- empirical use of an antifungal agent

If a patient fails to respond to topical antibiotics then the patient should be referred to ENT.

Malignant otitis externa is more common in elderly diabetics. In this condition, there is extension of infection into the bony ear canal and the soft tissues deep to the bony canal. Intravenous antibiotics may be required.

*many ENT doctors disagree with this and feel that concerns about ototoxicity are unfounded

# VERTIGO

Vertigo may be defined as the false sensation that the body or environment is moving.

The table below lists the main characteristics of the most important causes of vertigo

| Disorder | Notes |
|---|---|
| **Viral labyrinthitis** | Recent viral infection<br>Sudden onset<br>Nausea and vomiting<br>Hearing may be affected |
| **Vestibular neuronitis** | Recent viral infection<br>Recurrent vertigo attacks lasting hours or days<br>No hearing loss |
| **Benign paroxysmal positional vertigo** | Gradual onset<br>Triggered by change in head position<br>Each episode lasts 10-20 seconds |
| **Meniere's disease** | Associated with hearing loss, tinnitus and sensation of fullness or pressure in one or both ears |
| **Vertebrobasilar ischaemia** | Elderly patient<br>Dizziness on extension of neck |
| **Acoustic neuroma** | Hearing loss, vertigo, tinnitus<br>Absent corneal reflex is important sign<br>Associated with neurofibromatosis type 2 |

Other causes of vertigo include
- posterior circulation stroke
- trauma
- multiple sclerosis
- ototoxicity e.g. gentamicin

# BENIGN PAROXYSMAL POSITIONAL VERTIGO

Benign paroxysmal positional vertigo (BPPV) is one of the most common causes of vertigo encountered. It is characterised by the sudden onset of dizziness and vertigo triggered by changes in head position. The average age of onset is 55 years and it is less common in younger patients.

Features
- vertigo triggered by change in head position (e.g. rolling over in bed or gazing upwards)
- may be associated with nausea
- each episode typically lasts 10-20 seconds
- positive Dix-Hallpike manoeuvre

BPPV has a good prognosis and usually resolves spontaneously after a few weeks to months. Symptomatic relief may be gained by:
- **Epley manoeuvre** (successful in around 80% of cases)
- teaching the patient exercises they can do themselves at home, termed vestibular rehabilitation, for example Brandt-Daroff exercises

Medication is often prescribed (e.g. Betahistine) but it tends to be of limited value.

Around half of people with BPPV will have a recurrence of symptoms 3–5 years after their diagnosis

# VESTIBULAR NEURONITIS

Vestibular neuronitis is a cause of vertigo that often develops following a viral infection.

Features
- recurrent vertigo attacks lasting hours or days
- nausea and vomiting may be present
- horizontal nystagmus is usually present
- no hearing loss or tinnitus

Differential diagnosis
- viral labyrinthitis
- posterior circulation stroke: the HiNTs exam can be used to distinguish vestibular neuronitis from posterior circulation stroke

Management
- vestibular rehabilitation exercises are the preferred treatment for patients who experience chronic symptoms
- buccal or intramuscular prochlorperazine is often used to provide rapid relief for severe cases
- a short oral course of prochlorperazine, or an antihistamine (cinnarizine, cyclizine, or promethazine) may be used to alleviate less severe cases

# VESTIBULAR SCHWANNOMA (ACOUSTIC NEUROMA)

Vestibular schwannomas (sometimes referred to as acoustic neuromas) account for approximately 5% of intracranial tumours and 90% of cerebellopontine angle tumours.

The classical history of vestibular schwannoma includes a combination of vertigo, hearing loss, tinnitus and an absent corneal reflex. Features can be predicted by the affected cranial nerves:
- cranial nerve VIII: vertigo, unilateral sensorineural hearing loss, unilateral tinnitus
- cranial nerve V: absent corneal reflex
- cranial nerve VII: facial palsy

Bilateral vestibular schwannomas are seen in neurofibromatosis type 2.

Patients with a suspected vestibular schwannoma should be referred urgently to ENT. It should be noted though that the tumours are often slow growing, benign and often observed initially.

MRI of the cerebellopontine angle is the investigation of choice. Audiometry is also important as only 5% of patients will have a normal audiogram.

Management is with either surgery, radiotherapy or observation.

# TINNITUS

Causes of tinnitus include:

| **Meniere's disease** | **Associated with hearing loss, vertigo, tinnitus and sensation of fullness or pressure in one or both ears** |
|---|---|
| **Otosclerosis** | Onset is usually at 20-40 years<br>Conductive deafness<br>Tinnitus<br>Normal tympanic membrane*<br>Positive family history |
| **Acoustic neuroma** | Hearing loss, vertigo, tinnitus<br>Absent corneal reflex is important sign<br>Associated with neurofibromatosis type 2 |
| **Hearing loss** | Causes include excessive loud noise and presbycusis |
| **Drugs** | Aspirin/NSAIDs<br>Aminoglycosides<br>Loop diuretics<br>Quinine |

Other causes include
- impacted ear wax
- chronic suppurative otitis media

*10% of patients may have a 'flamingo tinge', caused by hyperaemia

# MENIERE'S DISEASE

Meniere's disease is a disorder of the inner ear of unknown cause. It is characterised by excessive pressure and progressive dilation of the endolymphatic system. It is more common in middle-aged adults but may be seen at any age. Meniere's disease has a similar prevalence in both men and women.

Features

- recurrent episodes of vertigo, tinnitus and hearing loss (sensorineural). Vertigo is usually the prominent symptom
- a sensation of aural fullness or pressure is now recognised as being common
- other features include nystagmus and a positive Romberg test
- episodes last minutes to hours
- typically symptoms are unilateral but bilateral symptoms may develop after a number of years

Natural history

- symptoms resolve in the majority of patients after 5-10 years
- the majority of patients will be left with a degree of hearing loss
- psychological distress is common

Management

- ENT assessment is required to confirm the diagnosis
- patients should inform the DVLA. The current advice is to cease driving until satisfactory control of symptoms is achieved
- acute attacks: buccal or intramuscular prochlorperazine. Admission is sometimes required
- prevention: betahistine and vestibular rehabilitation exercises may be of benefit

## OTOSCLEROSIS

Otosclerosis describes the replacement of normal bone by vascular spongy bone. It causes a progressive conductive deafness due to fixation of the stapes at the oval window. Otosclerosis is autosomal dominant and typically affects young adults

Onset is usually at 20-40 years - features include:

- conductive deafness
- tinnitus
- normal tympanic membrane*
- positive family history

Management

- hearing aid
- stapedectomy

*10% of patients may have a 'flamingo tinge', caused by hyperaemia

# BRACHIAL NEURITIS

Brachial neuritis is characterized by acute onset of unilateral (occasionally bilateral) severe pain, followed by shoulder and scapular weakness several days later. Sensory changes are usually minimal. There may be subsequent rapid wasting of the arm muscles in accordance to which nerve is involved. Precipitating factors include recent trauma, infection, surgery, or even vaccination. Rarely it may be hereditary. The prognosis is usually good except when the phrenic nerve is involved since this can result in significant breathlessness.

# BRACHIAL PLEXUS INJURIES

Erb-Duchenne paralysis
- damage to C5,6 roots
- winged scapula
- may be caused by a breech presentation

Klumpke's paralysis
- damage to T1
- loss of intrinsic hand muscles
- due to traction

# BRAIN ABSCESS

Basics
- CNS abscesses may result from a number of causes including, extension of sepsis from middle ear or sinuses, trauma or surgery to the scalp, penetrating head injuries and embolic events from endocarditis

- The presenting symptoms will depend upon the site of the abscess (those in critical areas e.g.motor cortex) will present earlier. Abscesses have a considerable mass effect in the brain and raised intra cranial pressure is common.
- Although fever, headache and focal neurology are highly suggestive of a brain abscess the absence of one or more of these does not exclude the diagnosis, fever may be absent and even if present, is usually not the swinging pyrexia seen with abscesses at other sites.
- Assessment of the patient includes imaging with CT scanning.
- Treatment is usually surgical, a craniotomy is performed and the abscess cavity debrided. The abscess may reform because the head is closed following abscess drainage.

# BRAIN LESIONS

The following neurological disorders/features may allow localisation of a brain lesion:

**Gross anatomy**

Parietal lobe lesions

- sensory inattention
- apraxias
- astereognosis (tactile agnosia)
- inferior homonymous quadrantanopia
- Gerstmann's syndrome (lesion of dominant parietal): alexia, acalculia, finger agnosia and right-left disorientation

Occipital lobe lesions

- homonymous hemianopia (with macula sparing)
- cortical blindness
- visual agnosia

Temporal lobe lesion

- Wernicke's aphasia: this area 'forms' the speech before 'sending it' to Brocas area. Lesions result in word substituion, neologisms but speech remains fluent
- superior homonymous quadrantanopia
- auditory agnosia

- prosopagnosia (difficulty recognising faces)

Frontal lobes lesions

- expressive (Broca's) aphasia: located on the posterior aspect of the frontal lobe, in the inferior frontal gyrus. Speech is non-fluent, laboured, and halting
- disinhibition
- perseveration
- anosmia
- inability to generate a list

Cerebellum lesions

- midline lesions: gait and truncal ataxia
- hemisphere lesions: intention tremor, past pointing, dysdiadokinesis, nystagmus

**More specific areas**

| Area | Associated conditions |
|---|---|
| Medial thalamus and mammillary bodies of the hypothalamus | Wernicke and Korsakoff syndrome |
| Subthalamic nucleus of the basal ganglia | Hemiballism |
| Striatum (caudate nucleus) of the basal ganglia | Huntington chorea |
| Substantia nigra of the basal ganglia | Parkinson's disease |
| Amygdala | Kluver-Bucy syndrome (hypersexuality, hyperorality, hyperphagia, visual agnosia |

# CHOREA

Chorea describes involuntary, rapid, jerky movements which often move from one part of the body to another. Slower, sinuous movement of the limbs is termed athetosis. Chorea is caused by damage to the basal ganglia, especially the caudate nucleus.

Causes of chorea
- Huntington's disease, Wilson's disease, ataxic telangiectasia
- SLE, anti-phospholipid syndrome
- rheumatic fever: Sydenham's chorea
- drugs: oral contraceptive pill, L-dopa, antipsychotics
- neuroacanthocytosis
- pregnancy: chorea gravidarum
- thyrotoxicosis
- polycythaemia rubra vera
- carbon monoxide poisoning
- cerebrovascular disease

# HUNTINGTON'S DISEASE

Huntington's disease is an inherited neurodegenerative condition. It is a progressive and incurable condition that typically results in death 20 years after the initial symptoms develop.

Genetics
- autosomal dominant
- trinucleotide repeat disorder: repeat expansion of CAG
  - as Huntington's disease is a trinucleotide repeat disorder, the phenomenon of anticipation may be seen, where the disease is presents at an earlier age in successive generations
- results in degeneration of cholinergic and GABAergic neurons in the striatum of the basal ganglia
- due to defect in huntingtin gene on chromosome 4

Features typical develop after 35 years of age
- Chorea
- personality changes (e.g. irritability, apathy, depression) and intellectual impairment
- dystonia
- saccadic eye movements

# HEMIBALLISM

Hemiballism occurs following damage to the subthalamic nucleus. Ballisic movements are involuntary, sudden, jerking movements which occur contralateral to the side of the lesion. The ballisic movements primarily affect the proximal limb musculature whilst the distal muscles may display more choreiform-like movements

Symptoms may decrease whilst the patient is asleep.

Antidopaminergic agents (e.g. Haloperidol) are the mainstay of treatment

# HEADACHE

Headache accounts for a large proportion of medical consultations. The table below summarises the main characteristics of common or important causes:

| Condition | Notes |
|---|---|
| **Migraine** | Recurrent, severe headache which is usually unilateral and throbbing in nature<br>May be be associated with aura, nausea and photosensitivity<br>Aggravated by, or causes avoidance of, routine activities of daily living. Patients often describe 'going to bed'.<br>In women may be associated with menstruation |
| **Tension headache** | Recurrent, non-disabling, bilateral headache, often described as a 'tight-band'<br>Not aggravated by routine activities of daily living |
| **Cluster headache*** | Pain typical occurs once or twice a day, each episode lasting 15 mins - 2 hours with clusters typically lasting 4-12 weeks<br>Intense pain around one eye (recurrent attacks 'always' affect same side)<br>Patient is restless during an attack<br>Accompanied by redness, lacrimation, lid swelling<br>More common in men and smokers |
| **Temporal arteritis** | Typically patient > 60 years old<br>Usually rapid onset (e.g. < 1 month) of unilateral headache<br>Jaw claudication (65%)<br>Tender, palpable temporal artery<br>Raised ESR |
| **Medication overuse headache** | Present for 15 days or more per month<br>Developed or worsened whilst taking regular symptomatic medication<br>Patients using opioids and triptans are at most risk<br>May be psychiatric co-morbidity |

**Other causes of headache**

Acute single episode

- meningitis
- encephalitis
- subarachnoid haemorrhage
- head injury
- sinusitis
- glaucoma (acute closed-angle)
- tropical illness e.g. Malaria

Chronic headache

- chronically raised ICP
- Paget's disease
- psychological

*some neurologists use the term trigeminal autonomic cephalgia to group a number of conditions including cluster headache, paroxysmal hemicrania and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). It is recommended such patients are referred for specialist assessment as specific treatment may be required, for example it is known paroxysmal hemicrania responds very well to indomethacin

# MIGRAINE

Migraine is a common type of primary headache. It is characterised typically by:
- a severe, unilateral, throbbing headache
- associated with nausea, photophobia and phonophobia
- attacks may last up to 72 hours
- patients characteristically go to a darkened, quiet room during an attack
- 'classic' migraine attacks are precipitated by an aura. These occur in around one-third of migraine patients
- typical aura are visual, progressive, last 5-60 minutes and are characterised by transient hemianopic disturbance or a spreading scintillating scotoma
- formal diagnostic criteria are produced by the International Headache Society (see below)

Epidemiology
- 3 times more common in women
- prevalence in men is around 6%, in women 18%

Common triggers for a migraine attack
- tiredness, stress
- alcohol
- combined oral contraceptive pill
- lack of food or dehydration
- cheese, chocolate, red wines, citrus fruits
- menstruation
- bright lights

# MIGRAINE DIAGNOSTIC CRITERIA

The International Headache Society has produced the following diagnostic criteria for migraine without aura:

| **A** | **At least 5 attacks fulfilling criteria B-D** |
|---|---|
| **B** | Headache attacks lasting 4-72 hours* (untreated or unsuccessfully treated) |

| **A** | **At least 5 attacks fulfilling criteria B-D** |
|---|---|
| **C** | Headache has at least two of the following characteristics:<br>• 1. unilateral location*<br>• 2. pulsating quality (i.e., varying with the heartbeat)<br>• 3. moderate or severe pain intensity<br>• 4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) |
| **D** | During headache at least one of the following:<br>• 1. nausea and/or vomiting*<br>• 2. photophobia and phonophobia |
| **E** | Not attributed to another disorder (history and examination do not suggest a secondary headache disorder or, if they do, it is ruled out by appropriate investigations or headache attacks do not occur for the first time in close temporal relation to the other disorder) |

*In children, attacks may be shorter-lasting, headache is more commonly bilateral, and gastrointestinal disturbance is more prominent.

Migraine with aura (seen in around 25% of migraine patients) tends to be easier to diagnose with a typical aura being progressive in nature and may occur hours prior to the headache. Typical aura include a transient hemianopic disturbance or a spreading scintillating scotoma ('jagged crescent'). Sensory symptoms may also occur

If we compare these guidelines to the **NICE criteria** the following points are noted:
- NICE suggests migraines may be unilateral or bilateral
- NICE also give more detail about typical auras:

Auras may occur with or without headache and:
- are fully reversible
- develop over at least 5 minutes
- last 5-60 minutes

The following aura symptoms are atypical and may prompt further investigation/referral;
- motor weakness
- double vision
- visual symptoms affecting only one eye
- poor balance
- decreased level of consciousness.

# MIGRAINE: MANAGEMENT

It should be noted that as a general rule 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis. NICE produced guidelines in 2012 on the management of headache, including migraines.

Acute treatment
- first-line: offer combination therapy with an oral triptan and an NSAID, or an oral triptan and paracetamol
- for young people aged 12-17 years consider a nasal triptan in preference to an oral triptan
- if the above measures are not effective or not tolerated offer a non-oral preparation of metoclopramide* or prochlorperazine and consider adding a non-oral NSAID or triptan

Prophylaxis
- prophylaxis should be given if patients are experiencing 2 or more attacks per month. Modern treatment is effective in about 60% of patients.
- NICE advise either topiramate or propranolol 'according to the person's preference, comorbidities and risk of adverse events'. Propranolol should be used in preference to topiramate in women of child bearing age as it may be teratogenic and it can reduce the effectiveness of hormonal contraceptives
- if these measures fail NICE recommend 'a course of up to 10 sessions of acupuncture over 5-8 weeks'
- NICE recommend: 'Advise people with migraine that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people'
- for women with predictable menstrual migraine treatment NICE recommend either frovatriptan (2.5 mg twice a day) or zolmitriptan (2.5 mg twice or three times a day) as a type of 'mini-prophylaxis'
- pizotifen is no longer recommend. Adverse effects such as weight gain & drowsiness are common

*caution should be exercised with young patients as acute dystonic reactions may develop

# TRIPTANS

Triptans are specific 5-HT1B and 5-HT1D agonists used in the acute treatment of migraine. They are generally used first-line in combination therapy with an NSAID or paracetamol.

Prescribing points
- should be taken as soon as possible after the onset of headache, rather than at onset of aura
- oral, orodispersible, nasal spray and subcutaneous injections are available

Adverse effects

- 'triptan sensations' - tingling, heat, tightness (e.g. throat and chest), heaviness, pressure

Contraindications

- patients with a history of, or significant risk factors for, ischaemic heart disease or cerebrovascular disease

# MIGRAINE: PREGNANCY, CONTRACEPTION AND OTHER HORMONAL FACTORS

SIGN produced guidelines in 2008 on the management of migraine, the following is selected highlights:

Migraine during pregnancy

- paracetamol 1g is first-line
- NSAIDs can be used second-line in the first and second trimester
- avoid aspirin and opioids such as codeine during pregnancy

Migraine and the combined oral contraceptive (COC) pill

- if patients have migraine with aura then the COC is absolutely contraindicated due to an increased risk of stroke (relative risk 8.72)

Migraine and menstruation

- many women find that the frequency and severity of migraines increase around the time of menstruation
- SIGN recommends that women are treated with mefanamic acid or a combination of aspirin, paracetamol and caffeine. Triptans are also recommended in the acute situation

Migraine and hormone replacement therapy (HRT)

- safe to prescribe HRT for patients with a history of migraine but it may make migraines worse

# CLUSTER HEADACHE

Cluster headaches are known to be one of the most painful conditions that patients can have the misfortune to suffer. The name relates to the pattern of the headaches - they typically occur in clusters lasting several weeks, with the clusters themselves typically once a year.

Cluster headaches are more common in men (3:1) and smokers. Alcohol may trigger an attack and there also appears to be a relation to nocturnal sleep.

Features
- pain typical occurs once or twice a day, each episode lasting 15 mins - 2 hours
- clusters typically last 4-12 weeks
- intense sharp, stabbing pain around one eye (recurrent attacks 'always' affect same side)
- patient is restless and agitated during an attack
- accompanied by redness, lacrimation, lid swelling
- nasal stuffiness
- miosis and ptosis in a minority

Management
- acute: 100% oxygen (80% response rate within 15 minutes), subcutaneous triptan (75% response rate within 15 minutes)
- prophylaxis: verapamil is the drug of choice. There is also some evidence to support a tapering dose of prednisolone
- NICE recommend seeking specialist advice from a neurologist if a patient develops cluster headaches with respect to neuroimaging

Some neurologists use the term trigeminal autonomic cephalgia to group a number of conditions including cluster headache, paroxysmal hemicrania and short-lived unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT). It is recommended such patients are referred for specialist assessment as specific treatment may be required, for example it is known paroxysmal hemicrania responds very well to indomethacin

# MEDICATION OVERUSE HEADACHE

Medication overuse headache is one of the most common causes of chronic daily headache. It may affect up to 1 in 50 people

Features
- present for 15 days or more per month
- developed or worsened whilst taking regular symptomatic medication
- patients using opioids and triptans are at most risk
- may be psychiatric co-morbidity

Management (from 2008 SIGN guidelines)
- simple analgesics and triptans should be withdrawn abruptly (may initially worsen headaches)
- opioid analgesics should be gradually withdrawn

Withdrawal symptoms such as vomiting, hypotension, tachycardia, restlessness, sleep disturbances and anxiety may occur when medication is stopped

# POST-LUMBAR PUNCTURE HEADACHE

Headache following lumbar puncture (LP) occurs in approximately one-third of patients. The pathophysiology of is unclear but may relate to a 'leak' of CSF following dural puncture. Post-LP headaches are more common in young females with a low body mass index

Typical features

- usually develops within 24-48 hours following LP but may occur up to one week later
- may last several days
- worsens with upright position
- improves with recumbent position

| Factors which may contribute to headache | Factors which do not contribute to headache |
|---|---|
| Increased needle size<br>Direction of bevel<br>Not replacing the stylet<br>Increased number of LP attempts | Increased volume of CSF removed<br>Bed rest following procedure<br>Increased fluid intake post procedure<br>Opening pressure of CSF<br>Position of patient |

Management

- supportive initially (analgesia, rest)
- if pain continues for more than 72 hours then specific treatment is indicated, to prevent subdural haematoma
- treatment options include: blood patch, epidural saline and intravenous caffeine

# COMMON PERONEAL NERVE LESION

The sciatic nerve divides into the tibial and common peroneal nerves. Injury often occurs at the neck of the fibula

The most characteristic feature of a common peroneal nerve lesion is foot drop.

Other features include:
- weakness of foot dorsiflexion
- weakness of foot eversion
- weakness of extensor hallucis longus
- sensory loss over the dorsum of the foot and the lower lateral part of the leg
- wasting of the anterior tibial and peroneal muscles

# FOOT DROP

Foot drop is a result of weakness of the foot dorsiflexors.

Possible causes include:
- common peroneal nerve lesion - the most common cause
- L5 radiculopathy
- sciatic nerve lesion
- superficial or deep peroneal nerve lesion
- other possible includes central nerve lesions (e.g. stroke) but other features are usually present

A **common peroneal nerve lesion is the most common cause** . This is often secondary to compression at the neck of the fibula. This may be caused by certain positions such as leg crossing, squatting or kneeling. Prolonged confinement, recent weight loss, Baker's cysts and plaster casts to the lower leg are also known to be precipitating factors.

Examination
- if the patient has an isolated peroneal neuropathy there will be weakness of foot dorsiflexion and eversion. Reflexes will be normal
- weakness of hip abduction is suggestive of a L5 radiculopathy

Bilateral symptoms, fasiculations or other abnormal neurological findings (e.g. hyperreflexia) are indications for specialist referral.

If the examination suggests a peroneal neuropathy then conservative management is appropriate. Leg crossing, squatting and kneeling should be avoided. Symptoms typically improve over 2-3 months.*

*BMJ 2015;350:h1736 - Foot drop

# NEUROPATHIC PAIN

Neuropathic pain may be defined as pain which arises following damage or disruption of the nervous system. It is often difficult to treat and responds poorly to standard analgesia.

Examples include:
- diabetic neuropathy
- post-herpetic neuralgia
- trigeminal neuralgia
- prolapsed intervertebral disc

NICE updated their guidance on the management of neuropathic pain in 2013:
- first-line treatment*: amitriptyline, duloxetine, gabapentin or pregabalin
- if the first-line drug treatment does not work try one of the other 3 drugs
- tramadol may be used as 'rescue therapy' for exacerbations of neuropathic pain
- topical capsaicin may be used for localised neuropathic pain (e.g. post-herpetic neuralgia)
- pain management clinics may be useful in patients with resistant problems

*please note that for some specific conditions the guidance may vary. For example carbamazepine is used first-line for trigeminal neuralgia

# COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (CRPS) is the modern, umbrella term for a number of conditions such as reflex sympathetic dystrophy and causalgia. It describes a number of neurological and related symptoms which typically occur following surgery or a minor injury. CRPS is 3 times more common in women.

There are two types of CRPS:
- type I (most common): there is no demonstrable lesion to a major nerve
- type II: there is a lesion to a major nerve

Features
- progressive, disproportionate symptoms to the original injury/surgery
- allodynia
- temperature and skin colour changes
- oedema and sweating
- motor dysfunction
- the Budapest Diagnostic Criteria are commonly used in the UK

Management

- early physiotherapy is important
- neuropathic analgesia in-line with NICE guidelines
- specialist management (e.g. Pain team) is required

# CREUTZFELDT-JAKOB DISEASE

Creutzfeldt-Jakob disease (CJD) is rapidly progressive neurological condition caused by prion proteins. These proteins induce the formation of amyloid folds resulting in tightly packed beta-pleated sheets resistant to proteases.

Features
- dementia (rapid onset)
- myoclonus

Investigation
- CSF is usually normal
- EEG: biphasic, high amplitude sharp waves (only in sporadic CJD)
- MRI: hyperintense signals in the basal ganglia and thalamus

Sporadic CJD
- accounts for 85% of cases
- 10-15% of cases are familial
- mean age of onset is 65 years

New variant CJD
- younger patients (average age of onset = 25 years)
- psychological symptoms such as anxiety, withdrawal and dysphonia are the most common presenting features
- the 'prion protein' is encoded on chromosome 20 - it's role is not yet understood
- methionine homozygosity at codon 129 of the prion protein is a risk factor for developing CJD - all patients who have so far died have had this
- median survival = 13 months

Other prion diseases
- kuru
- fatal familial insomnia
- Gerstmann Straussler-Scheinker disease

# EPILEPSY: CLASSIFICATION

The basic classification of epilepsy has changed in recent years. The new basic seizure classification is based on 3 key features:

- Where seizures begin in the brain
- Level of awareness during a seizure (important as can affect safety during seizure)
- Other features of seizures

Focal seizures

- previously termed partial seizures
- these start in a specific area, on one side of the brain
- the level of awareness can vary in focal seizures. The terms focal aware (previously termed 'simple partial'), focal impaired awareness (previously termed 'complex partial') and awareness unknown are used to further describe focal seizures
- further to this, focal seizures can be classified as being motor (e.g. Jacksonian march), non-motor (e.g. déjà vu, jamais vu; ) or having other features such as aura

Generalised

- these engage or involve networks on both sides of the brain at the onset
- consciousness lost immediately. The level of awareness in the above classification is therefore not needed, as all patients lose consciousness
- generalised seizures can be further subdivided into motor (e.g. tonic-clonic) and non-motor (e.g. absence)
- specific types include:
- → tonic-clonic (grand mal)
- → tonic
- → clonic
- → typical absence (petit mal)
- → atonic

Unknown onset

- this termed is reserved for when the origin of the seizure is unknown

Focal to bilateral seizure

- starts on one side of the brain in a specific area before spreading to both lobes
- previously termed secondary generalized seizures

# EPILEPSY: LOCALISING FEATURES OF FOCAL SEIZURES

| Location | Typical seizure type |
|---|---|
| Temporal lobe (HEAD) | Hallucinations (auditory/gustatory/olfactory), Epigastric rising/Emotional, Automatisms (lip smacking/grabbing/plucking), Deja vu/Dysphasia post-ictal) |
| Frontal lobe (motor) | Head/leg movements, posturing, post-ictal weakness, Jacksonian march |
| Parietal lobe (sensory) | Paraesthesia |
| Occipital lobe (visual) | Floaters/flashes |

# EPILEPSY: TREATMENT

Most neurologists now start antiepileptics following a second epileptic seizure. NICE guidelines suggest starting antiepileptics after the first seizure if any of the following are present:
- the patient has a neurological deficit
- brain imaging shows a structural abnormality
- the EEG shows unequivocal epileptic activity
- the patient or their family or carers consider the risk of having a further seizure unacceptable

Sodium valproate is considered the first line treatment for patients with generalised seizures with carbamazepine used for focal seizures.

Generalised tonic-clonic seizures
- sodium valproate
- second line: lamotrigine, carbamazepine

Absence seizures* (Petit mal)
- sodium valproate or ethosuximide
- sodium valproate particularly effective if co-existent tonic-clonic seizures in primary generalised epilepsy

Myoclonic seizures**
- sodium valproate
- second line: clonazepam, lamotrigine

Focal seizures
- carbamazepine or lamotrigine
- second line: levetiracetam, oxcarbazepine or sodium valproate

*carbamazepine may exacerbate absence seizures

**carbamazepine may exacerbate myoclonic seizures

# STATUS EPILEPTICUS

This is a medical emergency. The priority is termination of seizure activity, which if prolonged will lead to irreversible brain damage. First-line drugs are benzodiazepines such as diazepam or lorazepam. If ineffective within 10 minutes it is appropriate to start a second-line agent such as phenytoin, sodium valproate, levetiracetam, or phenobarbital. If no response within 30 minutes from onset, then the best way to achieve rapid control of seizure activity is induction of general anaesthesia.

# PHENYTOIN

Phenytoin is used in the management of seizures.

Mechanism of action
- binds to sodium channels increasing their refractory period

**Adverse effects**

Phenytoin is associated with a large number of adverse effects. These may be divided into acute, chronic, idiosyncratic and teratogenic. Phenytoin is also an inducer of the P450 system.

Acute
- initially: dizziness, diplopia, nystagmus, slurred speech, ataxia
- later: confusion, seizures

Chronic
- common: gingival hyperplasia (secondary to increased expression of platelet derived growth factor, PDGF), hirsutism, coarsening of facial features, drowsiness
- megaloblastic anaemia (secondary to altered folate metabolism)
- peripheral neuropathy
- enhanced vitamin D metabolism causing osteomalacia
- lymphadenopathy
- dyskinesia

Idiosyncratic
- fever
- rashes, including severe reactions such as toxic epidermal necrolysis
- hepatitis
- Dupuytren's contracture*
- aplastic anaemia
- drug-induced lupus

Teratogenic
- associated with cleft palate and congenital heart disease

**Monitoring**

Phenytoin levels do not need to be monitored routinely but **trough levels, immediately before dose** should be checked if:
- adjustment of phenytoin dose
- suspected toxicity
- detection of non-adherence to the prescribed medication

*although not listed in the BNF

# CARBAMAZEPINE

Carbamazepine is chemically similar to the tricyclic antidepressant drugs. It is most commonly used in the treatment of epilepsy, particularly partial seizures, where carbamazepine remains a first-line medication. Other uses include
- trigeminal neuralgia
- bipolar disorder

Mechanism of action
- binds to sodium channels increases their refractory period

Adverse effects
- P450 enzyme inducer
- dizziness and ataxia
- drowsiness
- headache
- visual disturbances (especially diplopia)
- Steven-Johnson syndrome
- leucopenia and agranulocytosis
- hyponatraemia secondary to syndrome of inappropriate ADH secretion

Carbamazepine is known to exhibit autoinduction, hence when patients start carbamazepine they may see a return of seizures after 3-4 weeks of treatment.

# SODIUM VALPROATE

Sodium valproate is used in the management of epilepsy and is first-line therapy for generalised seizures. It works by increasing GABA activity.

Adverse effects
- P450 inhibitor
- gastrointestinal: nausea
- increased appetite and weight gain
- alopecia: regrowth may be curly
- ataxia
- tremor
- hepatotoxicity
- pancreatitis
- thrombocytopaenia
- teratogenic
- hyponatraemia
- hyperammonemic encephalopathy: L-carnitine may be used as treatment if this develops

## LAMOTRIGINE

Lamotrigine is an antiepileptic used second-line for a variety of generalised and partial seizures.

Mechanism of action
- sodium channel blocker

Adverse effects
- Stevens-Johnson syndrome

## TOPIRAMATE

Topiramate was developed as an antiepileptic and is used alone or as adjunctive treatment in generalised tonic-clonic seizures.

There appear to be multiple mechanisms of action:
- blocks voltage-gated Na+ channels
- increases GABA action
- carbonic anhydrase inhibition: this results in a decrease in urinary citrate excretion and formation of alkaline urine that favours the creation of calcium phosphate stone

Topiramate is an inducer of the P450 enzyme CYP3A4. This may result in hormonal contraception being less effective. As a result, the Faculty of Sexual and Reproductive Health (FSRH) suggests the following for patients taking topiramate:

- combined oral contraceptive pill and progestogen-only pill: UKMEC 3 (disadvantages outweigh advantages):
- implant: UKMEC 2 (advantages generally outweigh the disadvantages)

The injection (Depo-Provera) and intrauterine system are not affected by topiramate.

Adverse effects of topiramate include:

- reduced appetite and weight loss
- dizziness
- paraesthesia
- lethargy and poor concentration
- rare but important: acute myopia and secondary angle-closure glaucoma

Topiramate is associated with a risk of foetal malformations.

# EPILEPSY: PREGNANCY AND BREAST FEEDING

The risks of uncontrolled epilepsy during pregnancy generally outweigh the risks of medication to the fetus. All women thinking about becoming pregnant should be advised to take folic acid 5mg per day well before pregnancy to minimise the risk of neural tube defects. Around 1-2% of newborns born to non-epileptic mothers have congenital defects. This rises to 3-4% if the mother takes antiepileptic medication.

Other points

- aim for monotherapy
- there is no indication to monitor antiepileptic drug levels
- sodium valproate: associated with neural tube defects
- carbamazepine: often considered the least teratogenic of the older antiepileptics
- phenytoin: associated with cleft palate
- lamotrigine: studies to date suggest the rate of congenital malformations may be low. The dose of lamotrigine may need to be increased in pregnancy

Breast feeding is generally considered safe for mothers taking antiepileptics with the possible exception of the barbiturates

It is advised that pregnant women taking phenytoin are given vitamin K in the last month of pregnancy to prevent clotting disorders in the newborn

**Sodium valproate**

The November 2013 issue of the Drug Safety Update also carried a warning about new evidence showing a significant risk of neurodevelopmental delay in children following maternal use of sodium valproate.

The update concludes that sodium valproate should not be used during pregnancy and in women of childbearing age unless clearly necessary. Women of childbearing age should not start treatment without specialist neurological or psychiatric advice.

# NARCOLEPSY

Overview
- associated with HLA-DR2
- it is associated with low levels of orexin (hypocretin), a protein which is responsible for controlling appetite and sleep patterns
- early onset of REM sleep

Features
- typical onset in teenage years
- hypersomnolence
- cataplexy (sudden loss of muscle tone often triggered by emotion)
- sleep paralysis
- vivid hallucinations on going to sleep or waking up

Investigation
- multiple sleep latency EEG

Management
- daytime stimulants (e.g. modafinil) and nighttime sodium oxybate

# CATAPLEXY

Cataplexy describes the sudden and transient loss of muscular tone caused by strong emotion (e.g. laughter, being frightened). Around two-thirds of patients with narcolepsy have cataplexy.

Features range from buckling knees to collapse.

# EPILEPSY IN CHILDREN: SYNDROMES

Infantile spasms (West's syndrome)

- brief spasms beginning in first few (4-6) months of life; M>F
- Flexion of head, trunk, limbs → extension of arms (Salaam attack); last 1-2 secs, repeat up to 50 times
- Progressive mental handicap
- EEG: hypsarrhythmia
- usually 2nd to serious neurological abnormality (e.g. TS, encephalitis, birth asphyxia) or may be cryptogenic
- poor prognosis
- vigabatrin/steroids

Typical (petit mal) absence seizures

- onset 4-8 yrs
- duration few-30 secs; no warning, quick recovery; often many per day
- EEG: 3Hz generalized, symmetrical
- sodium valproate, ethosuximide
- good prognosis: 90-95% become seizure free in adolescence

Lennox-Gastaut syndrome

- may be extension of infantile spasms (50% have hx)
- onset 1-5 yrs
- atypical absences, falls, jerks
- 90% moderate-severe mental handicap
- EEG: slow spike
- ketogenic diet may help

Benign rolandic epilepsy

- most common in childhood, M>F
- paraesthesia (e.g. unilateral face), usually on waking up

Juvenile myoclonic epilepsy (Janz syndrome)

- onset: teens; F:M = 2:1
- Infrequent generalized seizures, often in morning
- Daytime absences
- Sudden, shock like myoclonic seizure (these may develop before seizures)
- usually good response to sodium valproate

Neonatal period - try vitamin B6

- 2nd: hypoglycaemia, meningitis, head trauma
- pyridoxine dependency (AR, IV B6)
- benign familial neonatal seizures (AD)
- benign neonatal convulsions (5th day)

# VIGABATRIN

Key points
- 40% of patients develop visual field defects, which may be irreversible
- visual fields should be checked every 6 months

# ABSENCE SEIZURES

Absence seizures (petit mal) are a form of generalised epilepsy that is mostly seen in children. The typical age of onset of 3-10 years old and girls are affected twice as commonly as boys

Features
- absences last a few seconds and are associated with a quick recovery
- seizures may be provoked by hyperventilation or stress
- the child is usually unaware of the seizure
- they may occur many times a day
- EEG: bilateral, symmetrical 3Hz spike and wave pattern

Management
- sodium valproate and ethosuximide are first-line treatment
- good prognosis - 90-95% become seizure free in adolescence

# ETHOSUXIMIDE

Ethosuximide is an antiepileptic that is particularly indicated in patients with absence seizures

Mechanism of action
- blocks T-type calcium channels in thalamic neurons

# GUILLAIN-BARRE SYNDROME

Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically Campylobacter jejuni)

Pathogenesis
- cross reaction of antibodies with gangliosides in the peripheral nervous system
- correlation between anti-ganglioside antibody (e.g. anti-GM1) and clinical features has been demonstrated
- anti-GM1 antibodies in 25% of patients

Miller Fisher syndrome
- variant of Guillain-Barre syndrome
- associated with ophthalmoplegia, areflexia and ataxia. The eye muscles are typically affected first
- usually presents as a descending paralysis rather than ascending as seen in other forms of Guillain-Barre syndrome
- anti-GQ1b antibodies are present in 90% of cases

# GUILLAIN-BARRE SYNDROME: FEATURES

Guillain-Barre syndrome describes an immune-mediated demyelination of the peripheral nervous system often triggered by an infection (classically Campylobacter jejuni).

The characteristic features of Guillain-Barre syndrome is progressive weakness of all four limbs. The weakness is classically ascending i.e. the lower extremities are affected first, however it tends to affect proximal muscles earlier than the distal ones. Sensory symptoms tend to be mild (e.g. distal paraesthesia) with very few sensory signs. Some patients experience back pain in the initial stages of the illness

Other features
- there may be a history of gastroenteritis
- areflexia
- cranial nerve involvement e.g. diplopia
- autonomic involvement: e.g. urinary retention, diarrhoea

Less common findings
- papilloedema: thought to be secondary to reduced CSF resorption

Investigations
- lumbar puncture

    - rise in protein with a normal white blood cell count (albuminocytologic dissociation) - found in 66%
- nerve condution studies may be performed

## GUILLAIN-BARRE SYNDROME: MANAGEMENT

Guillain-Barre syndrome describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically Campylobacter jejuni).

Management
- plasma exchange
- IV immunoglobulins (IVIG): as effective as plasma exchange. No benefit in combining both treatments. IVIG may be easier to administer and tends to have fewer side-effects
- steroids and immunosuppressants have not been shown to be beneficial
- FVC regularly to monitor respiratory function

Prognosis
- severe motor problems persist in about 15%
- around 5% die

## GUILLAIN-BARRE SYNDROME: PROGNOSIS

Guillain-Barre syndrome (GBS) describes an immune mediated demyelination of the peripheral nervous system often triggered by an infection (classically Campylobacter jejuni)

Poor prognostic features
- age > 40 years
- poor upper extremity muscle strength
- previous history of a diarrhoeal illness (specifically Campylobacter jejuni)
- high anti-GM1 antibody titre
- need for ventilatory support

There is currently contradictory evidence as to whether a gradual or rapid onset of GBS is associated with a poor outcome

# HEAD INJURY: TYPES OF TRAUMATIC BRAIN INJURY

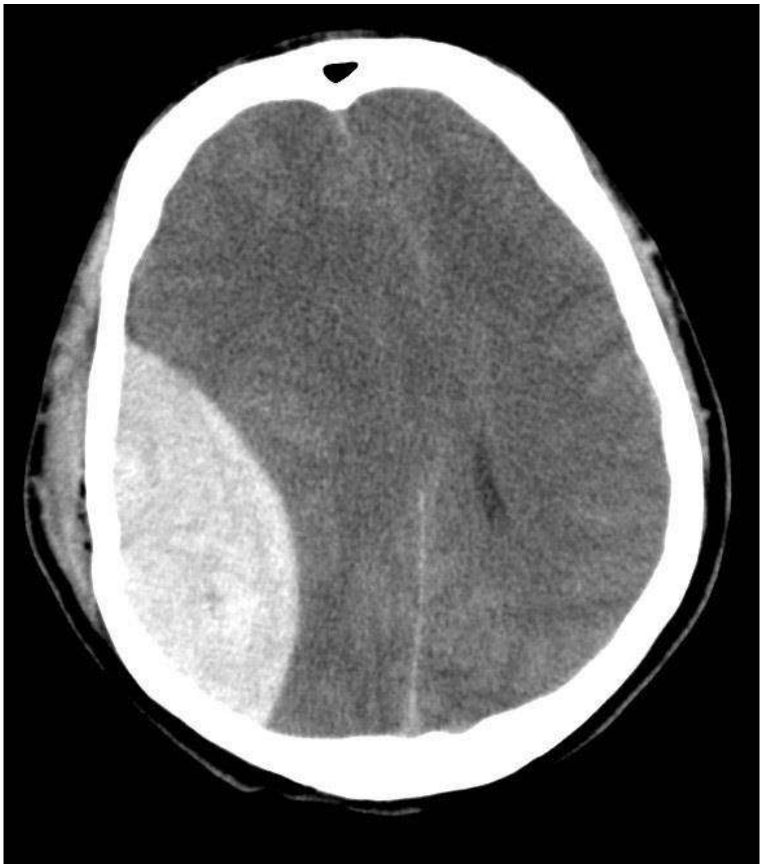
Basics

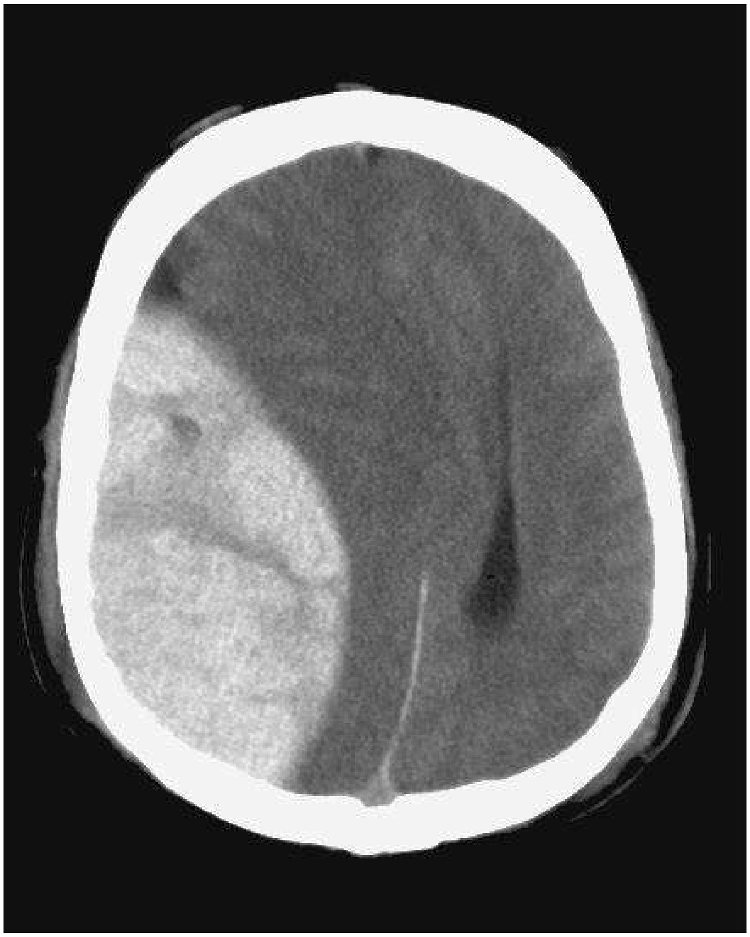
- primary brain injury may be focal (contusion/haematoma) or diffuse (diffuse axonal injury)
- diffuse axonal injury occurs as a result of mechanical shearing following deceleration, causing disruption and tearing of axons
- intra-cranial haematomas can be extradural, subdural or intracerebral, while contusions may occur adjacent to (coup) or contralateral (contre-coup) to the side of impact
- secondary brain injury occurs when cerebral oedema, ischaemia, infection, tonsillar or tentorial herniation exacerbates the original injury. The normal cerebral auto regulatory processes are disrupted following trauma rendering the brain more susceptible to blood flow changes and hypoxia
- the Cushings reflex (hypertension and bradycardia) often occurs late and is usually a pre terminal event

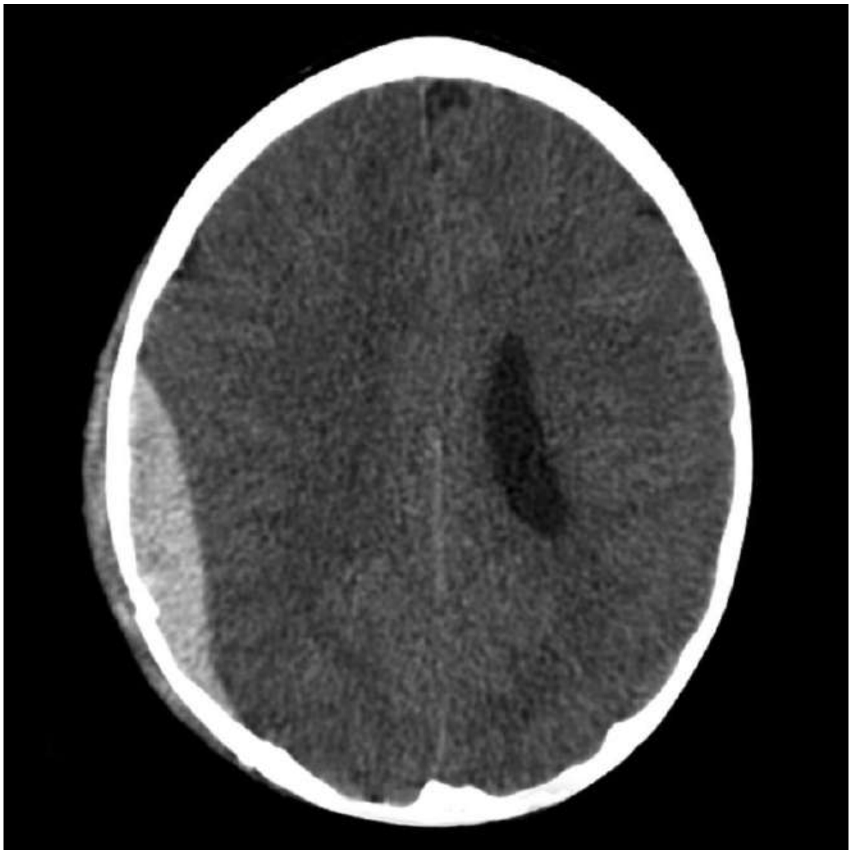
| Type of injury | Notes |
|---|---|
| **Extradural (epidural) haematoma** | Bleeding into the space between the dura mater and the skull. Often results from acceleration-deceleration trauma or a blow to the side of the head. The majority of epidural haematomas occur in the temporal region where skull fractures cause a rupture of the middle meningeal artery.<br>Features<br>• features of raised intracranial pressure<br>• some patients may exhibit a lucid interval |
| **Subdural haematoma** | Bleeding into the outermost meningeal layer. Most commonly occur around the frontal and parietal lobes.<br>Risk factors include old age, alcoholism and anticoagulation.<br>Slower onset of symptoms than a epidural haematoma. There may be fluctuating confusion/consciousness |
| **Subarachnoid haemorrhage** | Classically causes a sudden occipital headache. Usually occurs spontaneously in the context of a ruptured cerebral aneurysm but may be seen in association with other injuries when a patient has sustained a traumatic brain injury |

**Image gallery**

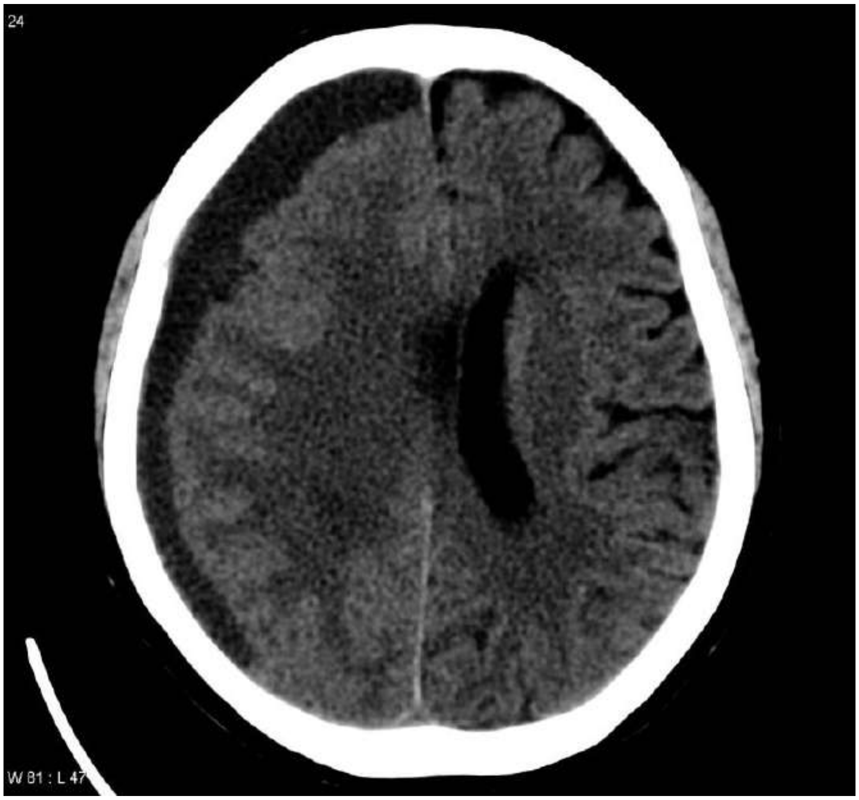
Extradural (epidural) haematoma:

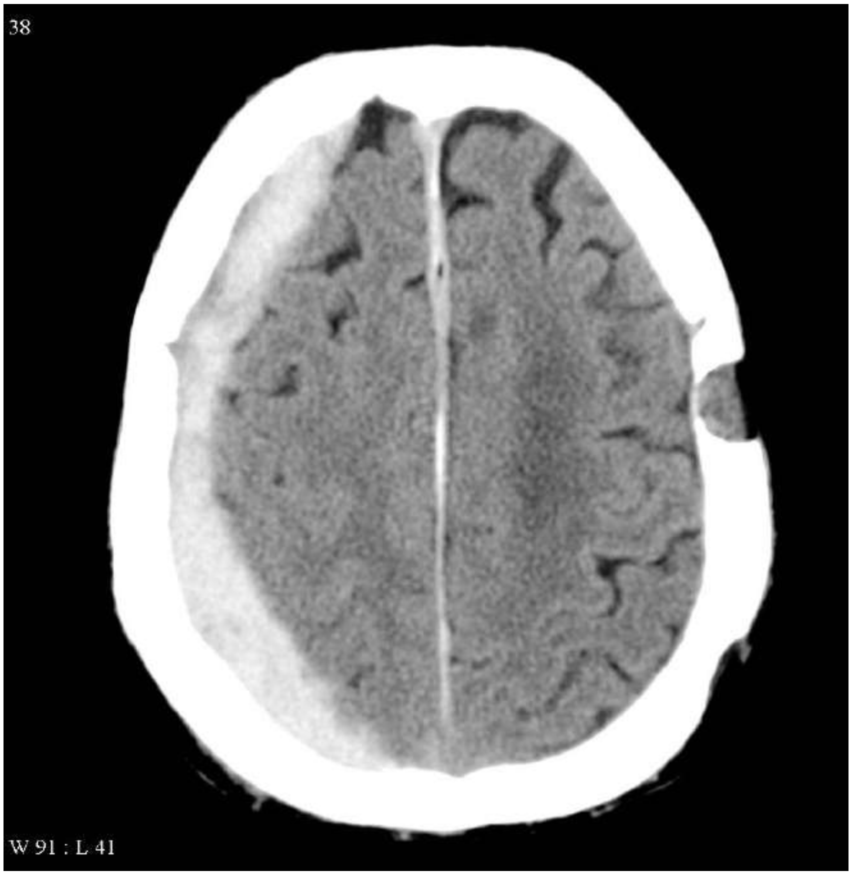




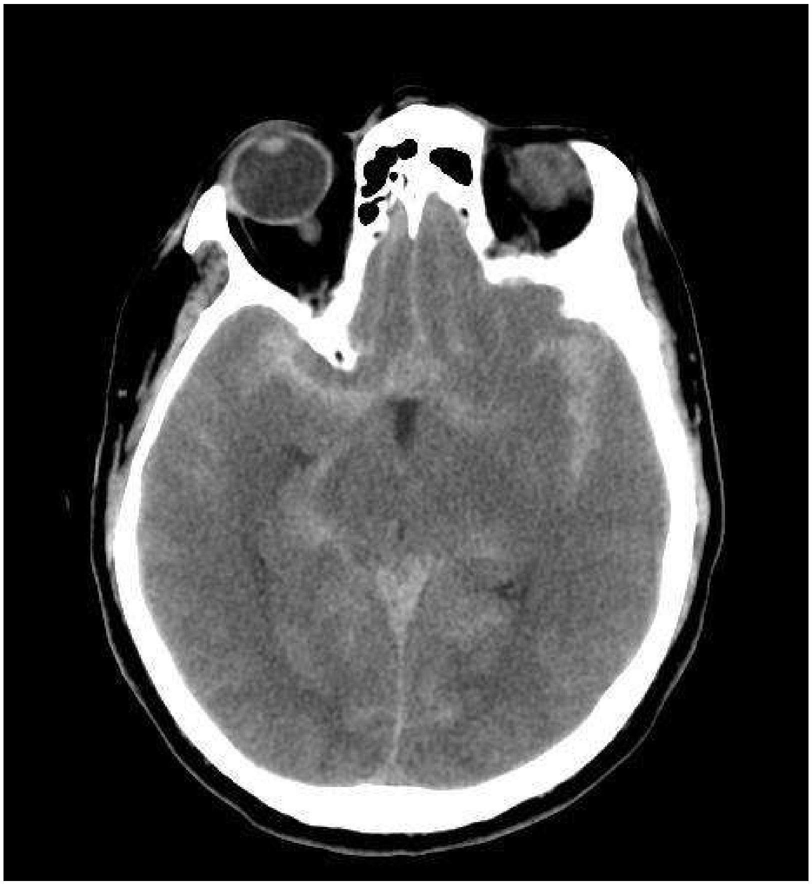


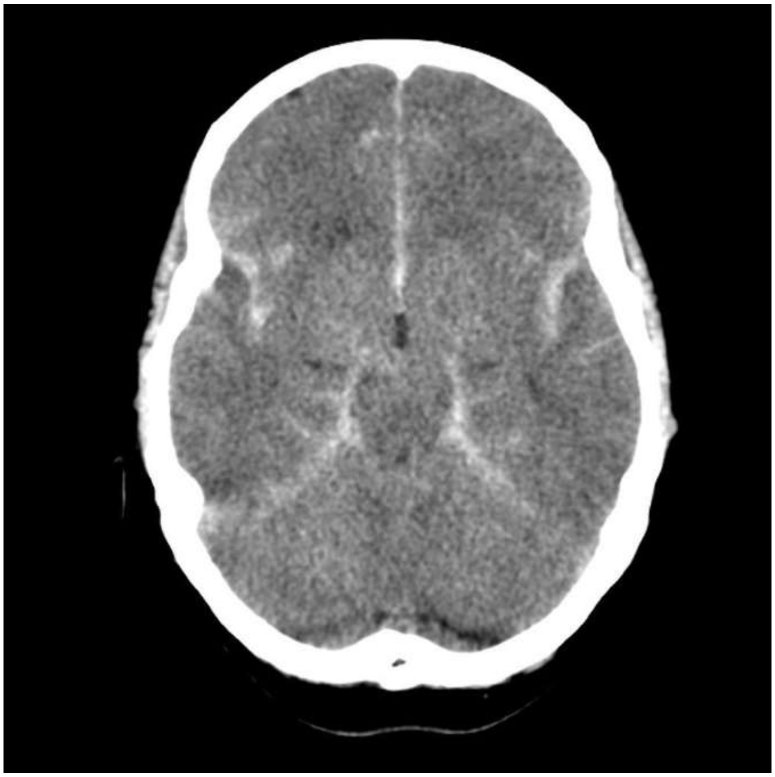
Subdural haematoma:





Subarachnoid haemorrhage:





# HEAD INJURY: NICE GUIDANCE ON INVESTIGATION

NICE has strict and clear guidance regarding which adult patients are safe to discharge and which need further CT head imaging. The latter group are also divided into two further cohorts, those who require an immediate CT head and those requiring CT head within 8 hours of injury:

CT head immediately

- GCS < 13 on initial assessment
- GCS < 15 at 2 hours post-injury
- suspected open or depressed skull fracture.
- any sign of basal skull fracture (haemotympanum, 'panda' eyes, cerebrospinal fluid leakage from the ear or nose, Battle's sign).
- post-traumatic seizure.
- focal neurological deficit.
- more than 1 episode of vomiting

CT head scan within 8 hours of the head injury - for adults with any of the following risk factors who have experienced some loss of consciousness or amnesia since the injury:

- age 65 years or older
- any history of bleeding or clotting disorders
- dangerous mechanism of injury (a pedestrian or cyclist struck by a motor vehicle, an occupant ejected from a motor vehicle or a fall from a height of greater than 1 metre or 5 stairs)

- more than 30 minutes' retrograde amnesia of events immediately before the head injury

If a patient is on warfarin who have sustained a head injury with no other indications for a CT head scan, perform a CT head scan within 8 hours of the injury.

# INTRACRANIAL HAEMORRHAGE

An intracranial haemorrhage describes a collection of blood or active process of bleeding within the skull. There are several types that are divided by the anatomical compartment in which they are found:

| | |
|---|---|
| **Extradural haematoma** | An extradural haematoma is a collection of blood between the skull and the dura. It is caused by low-impact trauma and classically presents with a loss of consciousness, a lucid interval and then a rapid decline in consciousness. Mass effect on the brain will cause uncal herniation and a fixed, dilated pupil due to third cranial nerve compression. CT imaging features are a hyperdense (bright), biconvex (or lentiform) collection around the surface of the brain. Definitive management is craniotomy and evacuation of the haematoma. |
| **Acute subdural haematoma** | An acute subdural haematoma is a fresh collection of blood that is under the layer of the dura mater of the meninges. It is most commonly caused by trauma but can be caused by vascular lesions (e.g. arteriovenous malformations). It is typically caused by high-speed injuries or acceleration-deceleration injuries and is therefore commonly associated with other brain injuries. There is a spectrum of severity of clinical presentation from an asymptomatic patient to those who are severely comatose. CT imaging will show a hyperdense (bright), crescenteric collection surrounding the brain that is not limited by suture lines. Definitive treatment is a decompressive craniectomy. |
| **Chronic subdural haematoma** | A chronic subdural haematoma is an old collection of blood that is under the layer of the dura mater of the meninges. It is more common in elderly patients, alcoholics, people on anticoagulation or in infants due to the fragility and/or predisposition of the bridging veins to bleed. Patients typically present several weeks after a mild head injury with progressive confusion, loss of consciousness, weakness or higher cortical function. CT imaging will show a hypodense (dark), crescenteric collection around the surface of the brain that is not limited by suture lines. In symptomatic patients, definitive treatment is burr hole drainage. |
| **Intracerebral haematoma** | An intracerebral (or intraparenchymal) haemorrhage is a collection of blood within the substance of the brain. Causes / risk factors include: hypertension, vascular lesion (e.g. aneurysm or arteriovenous malformation), cerebral amyloid angiopathy, brain tumour or infarct (particularly in stroke patients undergoing thrombolysis). Patients will present similarly to an ischaemic stroke (which is why it is crucial to obtain a CT in head in all stroke patients prior to thrombolysis) or with a decrease in consciousness. CT imaging will show a hyperdensity (bright lesion) within the substance of the brain. Treatment is often conservative under the care of stroke physicians, but large clots in patients with impaired consciousness may warrant surgical evacuation. |

| | |
|---|---|
| **Subarachnoid haemorrhage** | A subarachnoid haemorrhage is a bleed into the subarachnoid space which is deep to the subarachnoid layer of the meninges. The most common cause is trauma. In non-traumatic (‘spontaneous) subarachnoid haemorrhage, the most common cause is a ruptured aneurysm, but can be caused by an arteriovenous malformation, mycotic aneurysm, pituitary apoplexy or can be idiopathic. The classical presentation of sponataneous subarachnoid haemorrahge is a sudden-onset and severe headache, neck stiffness and photophobia. CT imaging will show hyperdensity within the cisterns or the brain and the sulci. In cases where the clinical diagnosis is certain but the CT imaging is inconclusive, a lumbar puncture should be performed after 12 hours to look for xanthocrhomia. Treatment is directed at the cause of the bleed. |
| **Intraventricular haemorrhage** | An intraventricular haemorrahge is a collection of blood within the ventricular system of the brain. In children it can occur due to the prematurity of the periventricular vascular structures. In adults it may be caused by an extension of subarachnoid haemorrhage, vascular lesions (e,g. aneurysms or arteriovenous malformations) or tumours. On CT imaging it appears as hyperdensity within the dark CSF spaces within the ventricles. Patients with intraventricular haemorrhage at risk of obstructive hydrocephalus and this would required surgical CSF diversion.<br>In neonatal practice the vast majority of IVH occur in the first 72 hours after birth, the aetiology is not well understood and it is suggested to occur as a result of birth trauma combined with cellular hypoxia, together the with the delicate neonatal CNS. |

# SUBDURAL HAEMORRHAGE

A subdural haematoma is a collection of blood deep to the dural layer of the meninges. The blood is not within the substance of the brain and is therefore called an ‘extra-axial’ or ‘extrinsic’ lesion. They can be unilateral or bilateral.

Subdural haematomas can be classified in terms of their age:
- Acute
- Subacute
- Chronic

Although the collection of blood is within the same anatomical compartment, acute and chronic subdurals have important differences in terms of their mechanisms, associated clinical features and management:

**Acute subdural haematoma**
An acute subdural haematoma is a collection of fresh blood within the subdural space and is most commonly caused by high-impact trauma. Since it is associated with high-impact injuries, there is often other brain underlying brain injuries.

There is a spectrum of severity of symptoms and presentation depending on the size of the compressive acute subdural haematoma and the associated injuries. Presentation ranges from an incidental finding in trauma to severe coma and coning due to herniation.

CT imaging is the first-line investigation and will show a crescentic collection, not limited by suture lines. They will appear hyperdense (bright) in comparison to the brain. Large acute subdural haematomas will push on the brain (‘mass effect’) and cause midline shift or herniation.

Small or incidental acute subdurals can be observed conservatively. Surgical options include monitoring of intracranial pressure and decompressive craniectomy.

**Chronic subdural haematoma**
A chronic subdural haematoma is a collection of blood within the subdural space that has been present for weeks to months.

Rupture of the small bridging veins within the subdural space rupture and cause slow bleeding. Elderly and alcoholic patients are particularly at risk of subdural haematomas since they have brain atrophy and therefore fragile or taut bridging veins.

Presentation is typically a several week to month progressive history of either confusion, reduced consciousness or neurological deficit.

Infants also have fragile bridging veins and can rupture in shaken baby syndrome.

On CT imaging they similarly are crescentic in shape, not restricted by suture lines and compress the brain (‘mass effect’). In contrast to acute subdurals, chronic subdurals are hypodense (dark) compared to the substance of the brain.

If the chronic subdural is an incidental finding or if it is small in size with no associated neurological deficit then it can be managed conservatively with the hope that it will dissolve with time. If the patient is confused, has an associated neurological deficit or has severe imaging findings then surgical decompression with burr holes is required.

# SUBARACHNOID HAEMORRHAGE

A subarachnoid haemorrhage (SAH) is an intracranial haemorrhage that is defined as the presence of blood within the subarachnoid space, i.e. deep to the subarachnoid layer of the meninges.

The most common cause of SAH is head injury and this is called traumatic SAH . In the absence of trauma, SAH is termed spontaneous SAH . The rest of this note focuses on spontaneous SAH.

Causes of spontaneous SAH include:

- Intracranial aneurysm* (saccular 'berry' aneurysms): this accounts for around 85% of cases. Conditions associated with berry aneurysms include adult polycystic kidney disease, Ehlers-Danlos syndrome and coarctation of the aorta
- Arteriovenous malformation
- Pituitary apoplexy
- Arterial dissection
- Mycotic (infective) aneurysms
- Perimesencephalic (an idiopathic venous bleed)

Classical presenting features include:

- Headache: typically sudden-onset ('thunderclap' or 'baseball bat'), severe ('worst of my life') and occipital
- Nausea and vomiting
- Meningism (photophobia, neck stiffness)
- Coma
- Seizures
- Sudden death
- ECG changes including ST elevation may be seen

Confirmation of SAH:

- Computed tomography (CT) head
    - Acute blood (hyperdense/bright on CT) is typically distributed in the basal cisterns, sulci and in severe cases the ventricular system.
    - CT is negative for SAH (no blood seen) in 7% of cases.
- Lumbar puncture (LP)
    - Used to confirm SAH if CT is negative.
    - LP is performed at least 12 hours following the onset of symptoms to allow the development of xanthochromia (the result of red blood cell breakdown).
    - Xanthochromia helps to distinguish true SAH from a 'traumatic tap' (blood introduced by the LP procedure).
    - As well as xanthochromia, CSF findings consistent with subarachnoid haemorrhage include a normal or raised opening pressure
- **Referral to neurosurgery to be made as soon as SAH is confirmed**

After spontaneous SAH is confirmed, the aim of investigation is to identify a causative pathology that needs urgent treatment:

- CT intracranial angiogram (to identify a vascular lesion e.g. aneurysm or AVM)
- +/- digital subtraction angiogram (catheter angiogram)

Treatment

- The treatment in spontaneous SAH is in accordance with the causative pathology
- Intracranial aneurysms are at risk of rebleeding and therefore require prompt intervention, preferably within 24 hours

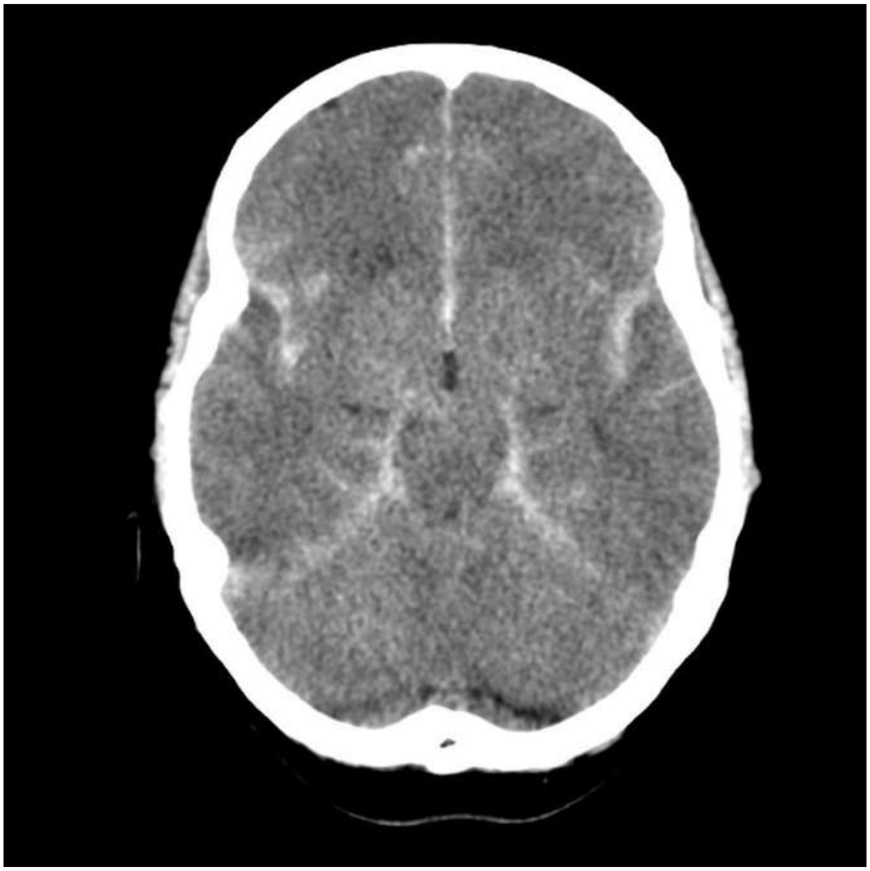
- Most intracranial aneurysms are now treated with a coil by interventional neuroradiologists, but a minority require a craniotomy and clipping by a neurosurgeon
- Until the aneurysm is treated, the patient should be kept on strict bed rest, well-controlled blood pressure and should avoid straining in order to prevent a re-bleed of the aneurysm
- Vasospasm is prevented using a 21-day course of nimodipine (a calcium channel inhibitor targeting the brain vasculature) and treated with hypervolaemia, induced-hypertension and haemodilution**
- Hydrocephalus is temporarily treated with an external ventricular drain (CSF diverted into a bag at the bedside) or, if required, a long-term ventriculo-peritoneal shunt

Complications of aneurysmal SAH:

- Re-bleeding (in around 30%)
- Vasospasm (also termed delayed cerebral ischaemia), typically 7-14 days after onset
- Hyponatraemia (most typically due to syndrome inappropriate anti-diuretic hormone (SIADH))
- Seizures
- Hydrocephalus
- Death

Important predictive factors in SAH:

- conscious level on admission
- age
- amount of blood visible on CT head



CT image shows diffuse subarachnoid haemorrhage in all basal cisterns, bilateral sylvian fissures and the inter-hemispheric fissure. This case demonstrates the typical distribution that takes the blood into the subarachnoid space in a subarachnoid hemorrhage.

*this may be secondary to either autonomic neural stimulation from the hypothalamus or elevated levels of circulating catecholamines

**the way nimodipine works in subarachnoid haemorrhage is not fully understood. It has been previously postulated that it reduces cerebral vasospasm (hence maintaining cerebral perfusion) but this has not been demonstrated in studies

# INTRACRANIAL VENOUS THROMBOSIS

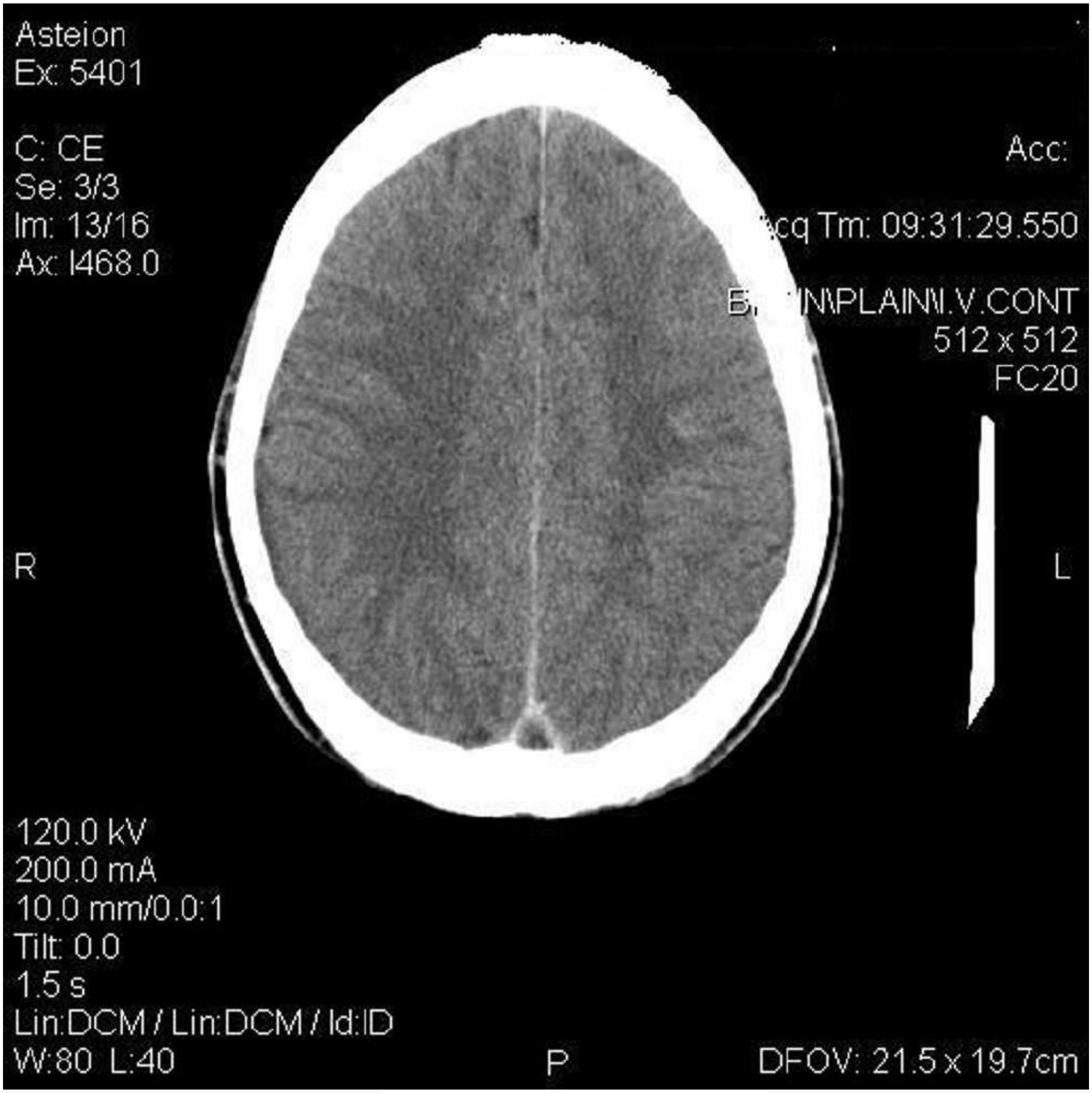
Overview
- can cause cerebral infarction, much lesson common than arterial causes
- 50% of patients have isolated sagittal sinus thromboses - the remainder have coexistent lateral sinus thromboses and cavernous sinus thromboses

Features
- headache (may be sudden onset)
- nausea & vomiting

Sagittal sinus thrombosis
- may present with seizures and hemiplegia
- parasagittal biparietal or bifrontal haemorrhagic infarctions are sometimes seen

Cavernous sinus thrombosis
- other causes of cavernous sinus syndrome: local infection (e.g. sinusitis), neoplasia, trauma
- periorbital oedema
- ophthalmoplegia: 6th nerve damage typically occurs before 3rd & 4th
- trigeminal nerve involvement may lead to hyperaesthesia of upper face and eye pain
- central retinal vein thrombosis

Lateral sinus thrombosis
- 6th and 7th cranial nerve palsies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N\PLAIN\I.V.CONT
512 x 512
FC20
R
L
120.0 kV
200.0 mA
10.0 mm/0.0:1
Tilt: 0.0
1.5 s
Lin:DCM / Lin:DCM / Id:ID
W:80 L:40
P
DFOV: 21.5 x 19.7cm

CT with contrast demonstrating a **superior sagittal sinus thrombosis** showing the typical empty delta sign. Look at the 'bottom' of the scan for the triangular shaped dural sinus. This should normally be white due to it being filled with contrast. The empty delta sign occurs when the thrombus fails to enhance within the dural sinus and is outlined by enhanced collateral channels in the falx. This sign is seen in only about 25%-30% of cases but is highly diagnostic for sagittal sinus thrombosis

# MENINGITIS

Most common adult cause (mortality)

- meningococcus (10%)
- pneumococcus (25%)

Diagnosis

- if partially treated with antibiotics, negative CSF culture, but glucose, protein and white cells unchanged

Neurological sequalae

- sensorineural hearing loss (most common)
- other neurological: epilepsy, paralysis
- infective: sepsis, intracerebral abscess
- pressure: brain herniation, hydrocephalus

# HERPES SIMPLEX ENCEPHALITIS

Herpes simplex (HSV) encephalitis is a common topic in the exam. The virus characteristically affects the temporal lobes - questions may give the result of imaging or describe temporal lobe signs e.g. aphasia

Features

- fever, headache, psychiatric symptoms, seizures, vomiting
- focal features e.g. aphasia
- peripheral lesions (e.g. cold sores) have no relation to presence of HSV encephalitis

Pathophysiology

- HSV-1 responsible for 95% of cases in adults
- typically affects temporal and inferior frontal lobes

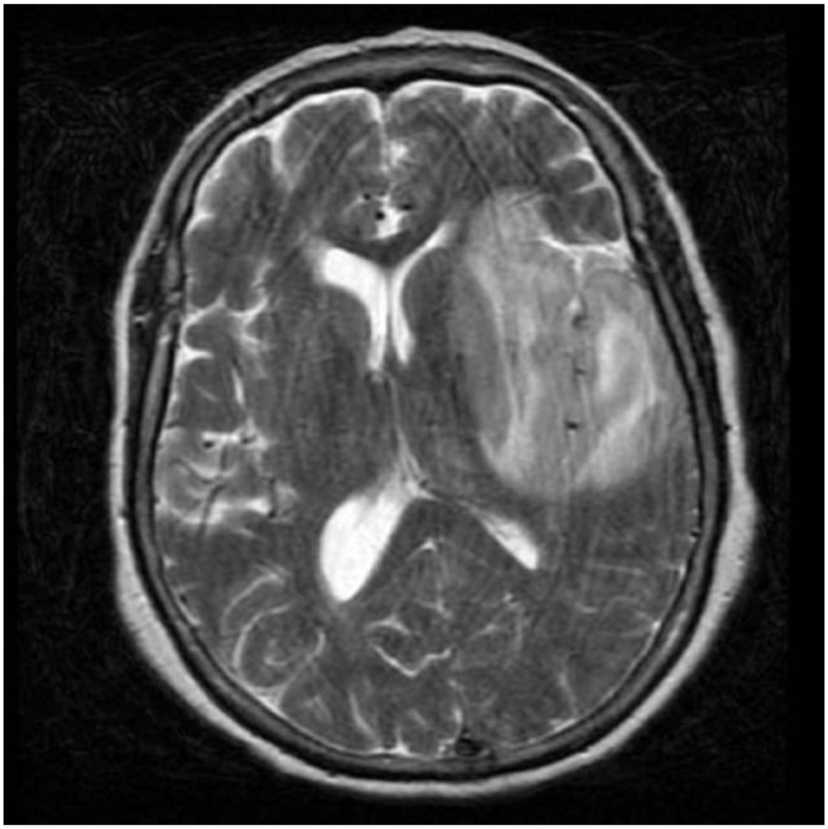
Investigation

- CSF: lymphocytosis, elevated protein
- PCR for HSV
- CT: medial temporal and inferior frontal changes (e.g. petechial haemorrhages) - normal in one-third of patients
- MRI is better
- EEG pattern: lateralised periodic discharges at 2 Hz

Treatment

- intravenous aciclovir

The prognosis is dependent on whether aciclovir is commenced early. If treatment is started promptly the mortality is 10-20%. Left untreated the mortality approaches 80%



MRI of a patient with HSV encephalitis. There is hyperintensity of the affected white matter and cortex in the medial temporal lobes and insular cortex.

# ACUTE DISSEMINATED ENCEPHALOMYELITIS

Acute disseminated encephalomyelitis (ADEM) is an autoimmune demylinating disease of the central nervous system. It may also be termed post infectious encephalomyelitis. The aetiology is not fully understood and it can occur following infection with a bacterial or viral pathogen. Common infections include measles, mumps, rubella, varicella and small pox, however this list is not exhaustive.

After a lag time of between a few days to 2 months there is an acute onset of multifocal neurological symptoms with rapid deterioration. Non-specific signs such as headache, fever, nausea and vomiting may also accompany the onset of illness. Motor and sensory deficits are frequent and there may also be brainstem involvement including occulomotor defects.

There are no specific biomarkers for the diagnosis of ADEM. MRI imaging may show areas of supra and infra-tentorial demylination. Management involves intravenous glucocorticoids and the consideration of IVIG where this fails.

## ANTI-NMDA RECEPTOR ENCEPHALITIS

Anti-NMDA receptor encephalitis is a paraneoplastic syndrome, presenting as prominent psychiatric features including agitation, hallucinations, delusions and disordered thinking; seizures, insomnia, dyskinesias and autonomic instability. Ovarian teratomas are detected in up to half of all female adult patients, particularly prevalent in Afro-Caribbean patients. MRI head can be normal but abnormalities can be visualised on FLAIR sequences in the deep subcortical limbic structures. CSF may demonstrate pleocytosis but can be normal initially. Anti-MuSK is an autoantibody specific to muscle kinase in myasthenia gravis with no evidence of a thymoma and without antibodies to acetylcholine receptors. Anti-GM1 is an autoantibody specific to acute inflammatory demyelinating polyneuropathy (AIDP) variant of Guillain-Barre syndrome.

Treatment of anti-NMDA encephalitis is based of immunosuppression with intravenous steroids, immunoglobulins, rituximab, cyclophosphamide or plasma exchange, alone or in combination. Resection of teratoma is also therapeutic.

# IDIOPATHIC INTRACRANIAL HYPERTENSION

Idiopathic intracranial hypertension (also known as pseudotumour cerebri and formerly benign intracranial hypertension) is a condition classically seen in young, overweight females.

Risk factors
- obesity
- female sex
- pregnancy
- drugs*: oral contraceptive pill, steroids, tetracycline, vitamin A, lithium

Features
- headache
- blurred vision
- papilloedema (usually present)
- enlarged blind spot
- sixth nerve palsy may be present

Management
- weight loss
- diuretics e.g. acetazolamide
- topiramate is also used, and has the added benefit of causing weight loss in most patients
- repeated lumbar puncture
- surgery: optic nerve sheath decompression and fenestration may be needed to prevent damage to the optic nerve. A lumboperitoneal or ventriculoperitoneal shunt may also be performed to reduce intracranial pressure

*if intracranial hypertension is thought to occur secondary to a known causes (e.g. Medication) then it is of course not idiopathic

# LAMBERT-EATON SYNDROME

Lambert-Eaton myasthenic syndrome is seen in association with small cell lung cancer and to a lesser extent breast and ovarian cancer. It may also occur independently as an autoimmune disorder. Lambert-Eaton myasthenic syndrome is caused by an antibody directed against presynaptic voltage-gated calcium channel in the peripheral nervous system.

Features

- repeated muscle contractions lead to increased muscle strength (in contrast to myasthenia gravis)
  - in reality, this is seen in only 50% of patients and following prolonged muscle use muscle strength will eventually decrease
- limb-girdle weakness (affects lower limbs first)
- hyporeflexia
- autonomic symptoms: dry mouth, impotence, difficulty micturating
- ophthalmoplegia and ptosis not commonly a feature (unlike in myasthenia gravis)

EMG

- incremental response to repetitive electrical stimulation

Management

- treatment of underlying cancer
- immunosuppression, for example with prednisolone and/or azathioprine
- 3,4-diaminopyridine is currently being trialled
  - works by blocking potassium channel efflux in the nerve terminal so that the action potential duration is increased. Calcium channels can then be open for a longer time and allow greater acetylcholine release to the stimulate muscle at the end plate
- intravenous immunoglobulin therapy and plasma exchange may be beneficial

# MACROGLOSSIA

Causes

- hypothyroidism
- acromegaly
- amyloidosis
- Duchenne muscular dystrophy
- mucopolysaccharidosis (e.g. Hurler syndrome)

Patients with Down's syndrome are now thought to have apparent macroglossia due to a combination of mid-face hypoplasia and hypotonia

# MOTOR NEURON DISEASE: TYPES

Motor neuron disease is a neurological condition of unknown cause which can present with both upper and lower motor neuron signs. It rarely presents before 40 years and various patterns of disease are recognised including amyotrophic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy and progressive bulbar palsy. In some patients however, there is a combination of clinical patterns

Amyotrophic lateral sclerosis (50% of patients)
- typically LMN signs in arms and UMN signs in legs
- in familial cases the gene responsible lies on chromosome 21 and codes for superoxide dismutase

Primary lateral sclerosis
- UMN signs only

Progressive muscular atrophy
- LMN signs only
- affects distal muscles before proximal
- carries best prognosis

Progressive bulbar palsy
- palsy of the tongue, muscles of chewing/swallowing and facial muscles due to loss of function of brainstem motor nuclei
- carries worst prognosis

# MOTOR NEURON DISEASE: FEATURES

Motor neuron disease is a neurological condition of unknown cause which can present with both upper and lower motor neuron signs. It rarely presents before 40 years and various patterns of disease are recognised including amyotrophic lateral sclerosis, progressive muscular atrophy and bulbar palsy.

There are a number of clues which point towards a diagnosis of motor neuron disease: fasciculations
- the absence of sensory signs/symptoms*
- the mixture of lower motor neuron and upper motor neuron signs
- wasting of the small hand muscles/tibialis anterior is common

Other features
- doesn't affect external ocular muscles

- no cerebellar signs
- abdominal reflexes are usually preserved and sphincter dysfunction if present is a late feature

The diagnosis of motor neuron disease is clinical, but nerve conduction studies will show normal motor conduction and can help exclude a neuropathy. Electromyography shows a reduced number of action potentials with increased amplitude. MRI is usually performed to exclude the differential diagnosis of cervical cord compression and myelopathy

*vague sensory symptoms may occur early in the disease (e.g. limb pain) but 'never' sensory signs

# ABSENT ANKLE JERKS, EXTENSOR PLANTARS

Typically caused by lesion producing both upper motor neuron (extensor plantars) and lower motor neuron (absent ankle jerk) signs

Causes
- subacute combined degeneration of the cord
- motor neuron disease
- Friedreich's ataxia
- syringomyelia
- taboparesis (syphilis)
- conus medullaris lesion

# MOTOR NEURON DISEASE: MANAGEMENT

Motor neuron disease is a neurological condition of unknown cause which can present with both upper and lower motor neuron signs. It rarely presents before 40 years and various patterns of disease are recognised including amyotrophic lateral sclerosis, progressive muscular atrophy and bulbar palsy

Riluzole
- prevents stimulation of glutamate receptors
- used mainly in amyotrophic lateral sclerosis
- prolongs life by about 3 months

Respiratory care
- non-invasive ventilation (usually BIPAP) is used at night
- studies have shown a survival benefit of around 7 months

Prognosis

- poor: 50% of patients die within 3 years

# SPASTIC PARAPARESIS

Spastic paraparesis describes a upper motor neuron pattern of weakness in the lower limbs

Causes
- demyelination e.g. multiple sclerosis
- cord compression: trauma, tumour
- parasagittal meningioma
- tropical spastic paraparesis
- transverse myelitis e.g. HIV
- syringomyelia
- hereditary spastic paraplegia
- osteoarthritis of the cervical spine

# AUTONOMIC NEUROPATHY

Features
- impotence, inability to sweat, postural hypotension
- postural hypotension e.g. drop of 30/15 mmHg
- loss of decrease in heart rate following deep breathing
- pupils: dilates following adrenaline instillation

Causes
- diabetes
- Guillain-Barre syndrome
- multisystem atrophy (MSA), Shy-Drager syndrome
- Parkinson's
- infections: HIV, Chagas' disease, neurosyphilis
- drugs: antihypertensives, tricyclics
- craniopharyngioma

# MULTIPLE SCLEROSIS

Multiple sclerosis is chronic cell-mediated autoimmune disorder characterised by demyelination in the central nervous system.

Epidemiology
- 3 times more common in women
- most commonly diagnosed in people aged 20-40 years
- much more common at higher latitudes (5 times more common than in tropics)

Genetics
- monozygotic twin concordance = 30%
- dizygotic twin concordance = 2%

A variety of subtypes have been identified:

Relapsing-remitting disease
- most common form, accounts for around 85% of patients
- acute attacks (e.g. last 1-2 months) followed by periods of remission

Secondary progressive disease
- describes relapsing-remitting patients who have deteriorated and have developed neurological signs and symptoms between relapses
- around 65% of patients with relapsing-remitting disease go on to develop secondary progressive disease within 15 years of diagnosis
- gait and bladder disorders are generally seen

Primary progressive disease
- accounts for 10% of patients
- progressive deterioration from onset
- more common in older people

# MULTIPLE SCLEROSIS: FEATURES

Patient's with multiple sclerosis (MS) may present with non-specific features, for example around 75% of patients have significant lethargy.

Diagnosis can be made on the basis of two or more relapses and either objective clinical evidence of two or more lesions or objective clinical evidence of one lesion together with reasonable historical evidence of a previous relapse.

Visual
- optic neuritis: common presenting feature
- optic atrophy
- Uhthoff's phenomenon: worsening of vision following rise in body temperature
- internuclear ophthalmoplegia

Sensory
- pins/needles
- numbness
- trigeminal neuralgia
- Lhermitte's syndrome: paraesthesiae in limbs on neck flexion

Motor
- spastic weakness: most commonly seen in the legs

Cerebellar
- ataxia: more often seen during an acute relapse than as a presenting symptom
- tremor

Others
- urinary incontinence
- sexual dysfunction
- intellectual deterioration

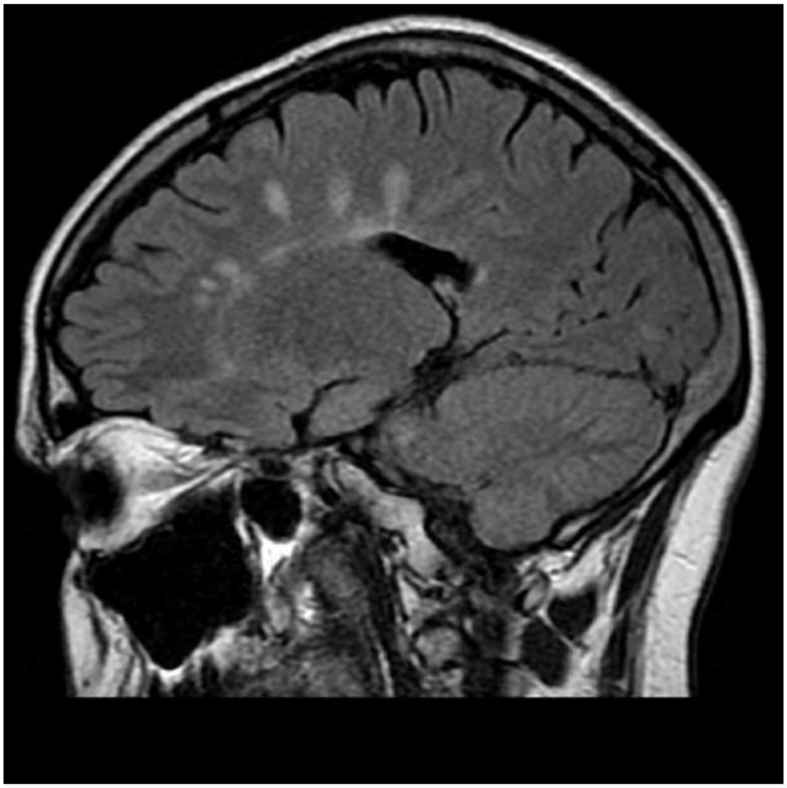
# MULTIPLE SCLEROSIS: INVESTIGATION

Diagnosis requires demonstration of lesions disseminated in time and space

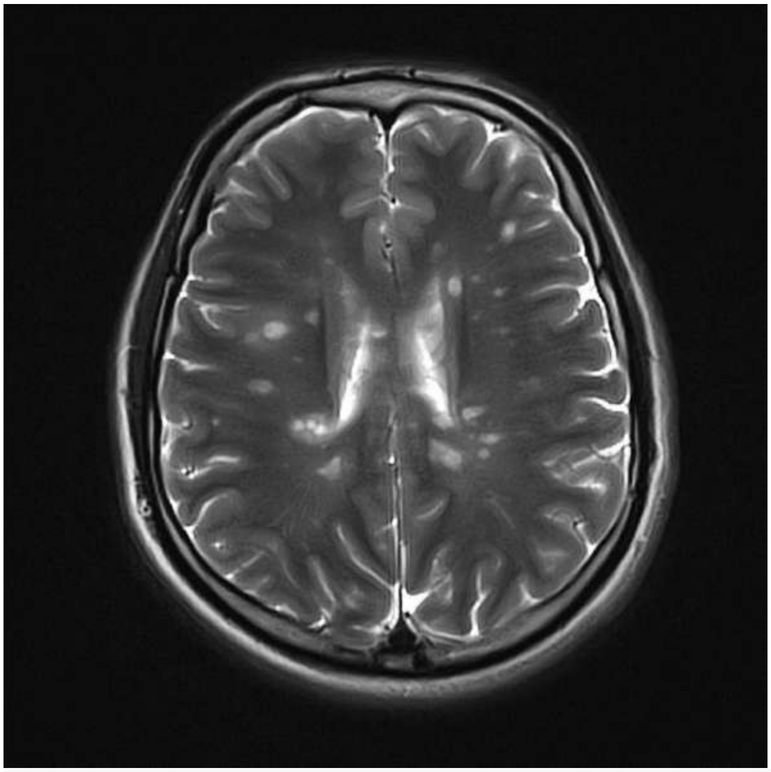
MRI
- high signal T2 lesions
- periventricular plaques
- Dawson fingers: often seen on FLAIR images - hyperintense lesions penpendicular to the corpus callosum

CSF
- oligoclonal bands (and not in serum)
- increased intrathecal synthesis of IgG

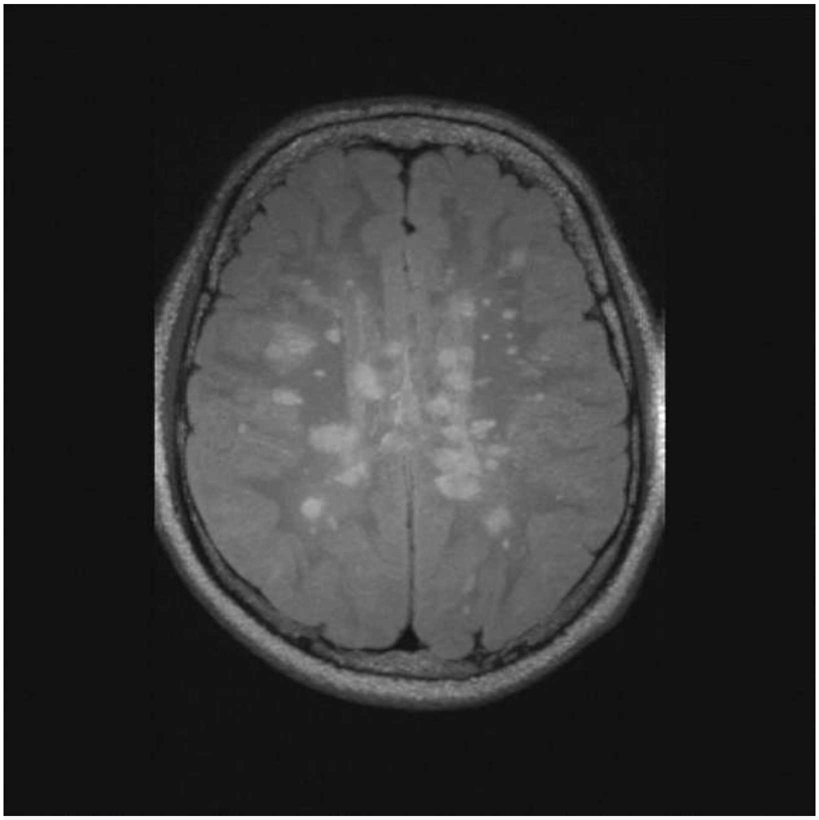
Visual evoked potentials
- delayed, but well preserved waveform



MRI showing multiple white matter plaques penpendicular to the corpus callosum giving the appearance of Dawson fingers



MRI from a young patient with multiple sclerosis. Widespread periventricular, juxtacortical, post fossa and upper cervical cord high T2 regions are noted. Note the difference in the lesions with varying degrees of contrast enhancement and restricted diffusion indicating active/recent demyelination. This satisfies the diagnostic criteria in terms of separation in terms of time space.



MRI FLAIR from the same patient as above. The numerous lesions are more easily identified than in the above T2 image.

# MULTIPLE SCLEROSIS: MANAGEMENT

Treatment in multiple sclerosis is focused at reducing the frequency and duration of relapses. There is no cure.

**Acute relapse**
High dose steroids (e.g. oral or IV methylprednisolone) may be given for 5 days to shorten the length of an acute relapse. It should be noted that steroids shorten the duration of a relapse and do not alter the degree of recovery (i.e. whether a patient returns to baseline function)

**Disease modifying drugs**
Beta-interferon has been shown to reduce the relapse rate by up to 30%. Certain criteria have to be met before it is used:

- relapsing-remitting disease + 2 relapses in past 2 years + able to walk 100m unaided
- secondary progressive disease + 2 relapses in past 2 years + able to walk 10m (aided or unaided)
- reduces number of relapses and MRI changes, however doesn't reduce overall disability

Other drugs used in the management of multiple sclerosis include:

- glatiramer acetate: immunomodulating drug - acts as an 'immune decoy'

- natalizumab: a recombinant monoclonal antibody that antagonises Alpha-4 Beta-1-integrin found on the surface of leucocytes, thus inhibiting migration of leucocytes across the endothelium across the blood-brain barrier
- fingolimod: sphingosine 1-phosphate receptor modulator, prevents lymphocytes from leaving lymph nodes. An oral formulation is available

**Some specific problems**

Fatigue

- once other problems (e.g. anaemia, thyroid or depression) have been excluded NICE recommend a trial of amantadine
- other options include mindfulness training and CBT

Spasticity

- baclofen and gabapentin are first-line. Other options include diazepam, dantrolene and tizanidine
- physiotherapy is important
- cannabis and botox are undergoing evalulation

Bladder dysfunction

- may take the form of urgency, incontinence, overflow etc
- guidelines stress the importance of getting an ultrasound first to assess bladder emptying - anticholinergics may worsen symptoms in some patients
- if significant residual volume → intermittent self-catheterisation
- if no significant residual volume → anticholinergics may improve urinary frequency

Oscillopsia (visual fields apper to oscillate)

- gabapentin is first-line

# BACLOFEN

Baclofen is used to treat muscle spasticity in conditions such as multiple sclerosis, cerebral palsy and spinal cord injuries.

Mechanism of action

- agonist of GABA receptors
- acts in the central nervous system (brain and spinal cord)

# MULTIPLE SCLEROSIS: PROGNOSTIC FEATURES

Good prognosis features

- female sex
- young age of onset (i.e. 20s or 30s)
- relapsing-remitting disease
- sensory symptoms only
- long interval between first two relapses
- complete recovery between relapses

Ways of remembering prognostic features
- the typical patient carries a better prognosis than an atypical presentation

# MULTIPLE SYSTEM ATROPHY

There are 2 predominant types of multiple system atrophy
1) MSA-P - Predominant Parkinsonian features
2) MSA-C - Predominant Cerebellar features

Shy-Drager syndrome is a type of multiple system atrophy.

Features
- parkinsonism
- autonomic disturbance
  - erectile dysfunction: often an early feature
  - postural hypotension
  - atonic bladder
- cerebellar signs

# TRANSVERSE MYELITIS

Causes of transverse myelitis
- viral infections: varicella-zoster, herpes simplex, cytomegalovirus, Epstein-Barr, influenza, echovirus, human immunodeficiency virus
- bacterial infections: syphilis, Lyme disease
- post-infectious (immune mediated)
- first symptom of multiple sclerosis (MS) or neuromyelitis optica (NMO)

# MYASTHENIA GRAVIS

Myasthenia gravis is an autoimmune disorder resulting in insufficient functioning acetylcholine receptors. Antibodies to acetylcholine receptors are seen in 85-90% of cases*. Myasthenia is more common in women (2:1)

The key feature is muscle fatigability - muscles become progressively weaker during periods of activity and slowly improve after periods of rest:

- extraocular muscle weakness: diplopia
- proximal muscle weakness: face, neck, limb girdle
- ptosis
- dysphagia

Associations

- thymomas in 15%
- autoimmune disorders: pernicious anaemia, autoimmune thyroid disorders, rheumatoid, SLE
- thymic hyperplasia in 50-70%

Investigations

- single fibre electromyography: high sensitivity (92-100%)
- CT thorax to exclude thymoma
- CK normal
- autoantibodies: around 85-90% of patients have antibodies to acetylcholine receptors. In the remaining patients, about about 40% are positive for anti-muscle-specific tyrosine kinase antibodies
- Tensilon test: IV edrophonium reduces muscle weakness temporarily - not commonly used anymore due to the risk of cardiac arrhythmia

Management

- long-acting anticholinesterase inhibitors e.g. pyridostigmine
- immunosuppression: prednisolone initially
- thymectomy

Management of myasthenic crisis

- plasmapheresis
- intravenous immunoglobulins

*antibodies are less commonly seen in disease limited to the ocular muscles

# MYASTHENIA GRAVIS: EXACERBATING FACTORS

The most common exacerbating factor is exertion resulting in fatigability, which is the hallmark feature of myasthenia gravis . Symptoms become more marked during the day

The following drugs may exacerbate myasthenia:

- penicillamine
- quinidine, procainamide
- beta-blockers
- lithium
- phenytoin
- antibiotics: gentamicin, macrolides, quinolones, tetracyclines

# MYOTONIC DYSTROPHY

Myotonic dystrophy (also called dystrophia myotonica) is an inherited myopathy with features developing at around 20-30 years old. It affects skeletal, cardiac and smooth muscle. There are two main types of myotonic dystrophy, DM1 and DM2.

Genetics

- autosomal dominant
- a trinucleotide repeat disorder
- DM1 is caused by a CTG repeat at the end of the DMPK (Dystrophia Myotonica-Protein Kinase) gene on chromosome 19
- DM2 is caused by a repeat expansion of the ZNF9 gene on chromosome 3

The key differences are listed in table below:

| DM1 | DM2 |
|---|---|
| - DMPK gene on chromosome 19<br>- Distal weakness more prominent | - ZNF9 gene on chromosome 3<br>- Proximal weakness more prominent<br>- Severe congenital form not seen |

General features

- myotonic facies (long, 'haggard' appearance)
- frontal balding
- bilateral ptosis
- cataracts
- dysarthria

Other features

- myotonia (tonic spasm of muscle)
- weakness of arms and legs (distal initially)
- mild mental impairment
- diabetes mellitus
- testicular atrophy
- cardiac involvement: heart block, cardiomyopathy
- dysphagia

# FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Facioscapulohumeral muscular dystrophy (FSHMD) is an autosomal dominant form of muscular dystrophy. As the name suggests it stypically affects the face, scapula and upper arms first. Symptoms typically presents by the age of 20 years.

# NECK LUMPS

The table below gives characteristic exam question features for conditions causing neck lumps:

| Condition | Notes |
|---|---|
| **Reactive lymphadenopathy** | By far the most common cause of neck swellings. There may be a history of local infection or a generalised viral illness |
| **Lymphoma** | Rubbery, painless lymphadenopathy<br>The phenomenon of pain whilst drinking alcohol is very uncommon<br>There may be associated night sweats and splenomegaly |
| **Thyroid swelling** | May be hypo-, eu- or hyperthyroid symptomatically<br>Moves upwards on swallowing |
| **Thyroglossal cyst** | More common in patients < 20 years old<br>Usually midline, between the isthmus of the thyroid and the hyoid bone<br>Moves upwards with protrusion of the tongue<br>May be painful if infected |
| **Pharyngeal pouch** | More common in older men<br>Represents a posteromedial herniation between thyropharyngeus and cricopharyngeus muscles<br>Usually not seen but if large then a midline lump in the neck that gurgles on palpation<br>Typical symptoms are dysphagia, regurgitation, aspiration and chronic cough |
| **Cystic hygroma** | A congenital lymphatic lesion (lymphangioma) typically found in the neck, classically on the left side<br>Most are evident at birth, around 90% present before 2 years of age |
| **Branchial cyst** | An oval, mobile cystic mass that develops between the sternocleidomastoid muscle and the pharynx<br>Develop due to failure of obliteration of the second branchial cleft in embryonic development<br>Usually present in early adulthood |
| **Cervical rib** | More common in adult females<br>Around 10% develop thoracic outlet syndrome |
| **Carotid aneurysm** | Pulsatile lateral neck mass which doesn't move on swallowing |

# THYROGLOSSAL CYST

The key to understanding thyroglossal cysts is to think about the name; thyro (thyroid) and glossal (tongue).

**Embryology**
The thyroid develops from the floor of the pharynx and descends into the neck during its development. It is connected to the tongue by the thyroglossal duct. The foramen cecum is the

point of attachment of the thyroglossal duct to the tongue. The thyroglossal duct normally atrophies but in some people may persist and give rise to a thyroglossal duct cyst.

**Presentations**
More common in patients < 20 years old.

Features

- usually midline, between the isthmus of the thyroid and the hyoid bone
- moves upwards with protrusion of the tongue
- may be painful if infected

# NEUROFIBROMATOSIS

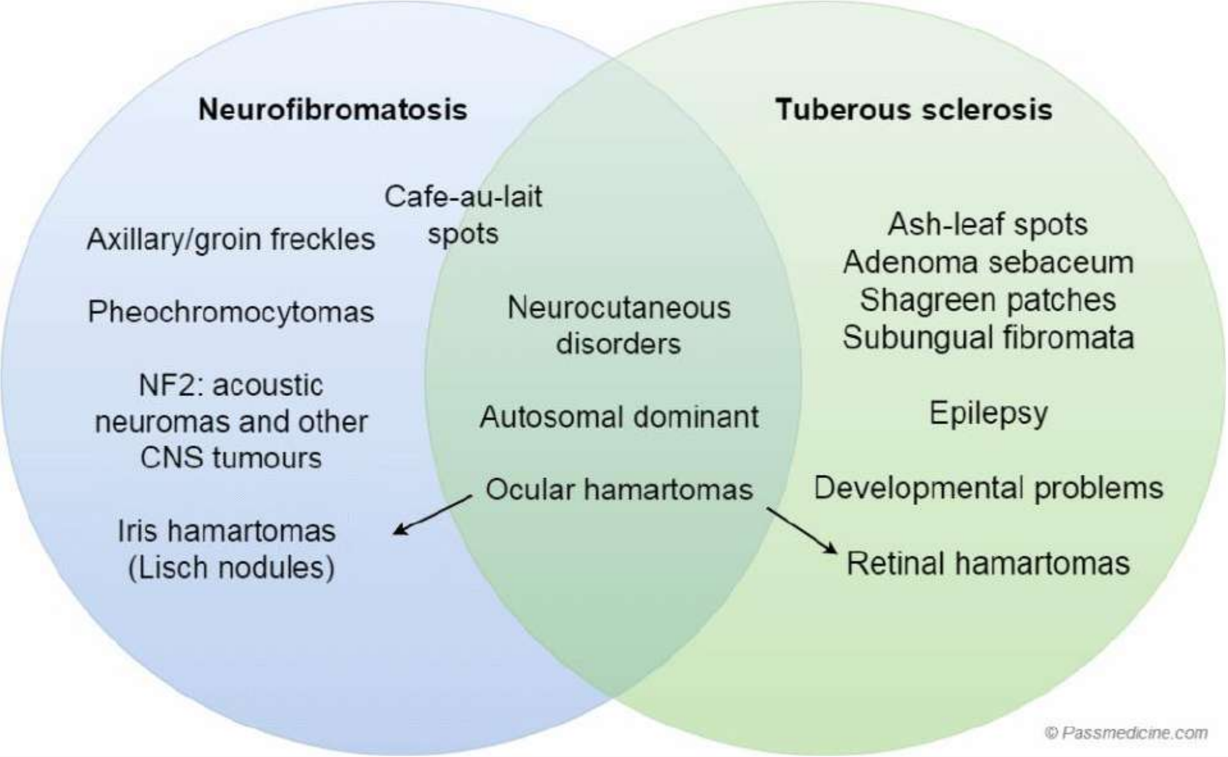
There are two types of neurofibromatosis, NF1 and NF2. Both are inherited in an autosomal dominant fashion

NF1 is also known as von Recklinghausen's syndrome. It is caused by a gene mutation on chromosome 17 which encodes neurofibromin and affects around 1 in 4,000

NF2 is caused by gene mutation on chromosome 22 and affects around 1 in 100,000

**Features**

| NF1 | NF2 |
|---|---|
| Café-au-lait spots (>= 6, 15 mm in diameter)<br>Axillary/groin freckles<br>Peripheral neurofibromas<br>Iris hamatomas (Lisch nodules) in > 90%<br>Scoliosis<br>Pheochromocytomas | Bilateral vestibular schwannomas<br>Multiple intracranial schwannomas, mengiomas and ependymomas |


Neurofibromatosis
Tuberous sclerosis
Cafe-au-lait spots
Axillary/groin freckles
Pheochromocytomas
NF2: acoustic neuromas and other CNS tumours
Iris hamartomas (Lisch nodules)
Neurocutaneous disorders
Autosomal dominant
Ocular hamartomas
Ash-leaf spots
Adenoma sebaceum
Shagreen patches
Subungual fibromata
Epilepsy
Developmental problems
Retinal hamartomas
© Passmedicine.com

Comparison of neurofibromatosis and tuberous sclerosis. Note that whilst they are both autosomal dominant neurocutaneous disorders there is little overlap otherwise

# TUBEROUS SCLEROSIS

Tuberous sclerosis (TS) is a genetic condition of autosomal dominant inheritance. Like neurofibromatosis, the majority of features seen in TS are neurocutaneous.

Cutaneous features

- depigmented 'ash-leaf' spots which fluoresce under UV light
- roughened patches of skin over lumbar spine (Shagreen patches)
- adenoma sebaceum (angiofibromas): butterfly distribution over nose
- fibromata beneath nails (subungual fibromata)
- café-au-lait spots* may be seen

Neurological features

- developmental delay
- epilepsy (infantile spasms or partial)
- intellectual impairment

Also

- retinal hamartomas: dense white areas on retina (phakomata)
- rhabdomyomas of the heart
- gliomatous changes can occur in the brain lesions
- polycystic kidneys, renal angiomyolipomata
- lymphangioleiomyomatosis: multiple lung cysts

*these of course are more commonly associated with neurofibromatosis. However a 1998 study of 106 children with TS found café-au-lait spots in 28% of patients

# LATERAL MEDULLARY SYNDROME

Lateral medullary syndrome, also known as Wallenberg's syndrome, occurs following occlusion of the posterior inferior cerebellar artery.

Cerebellar features

- ataxia
- nystagmus

Brainstem features

- ipsilateral: dysphagia, facial numbness, cranial nerve palsy e.g. Horner's
- contralateral: limb sensory loss

# PARANEOPLASTIC SYNDROMES AFFECTING NERVOUS SYSTEM

Lambert-Eaton myasthenic syndrome
- associated with small cell lung cancer (also breast and ovarian)
- antibody directed against pre-synaptic voltage gated calcium channel in the peripheral nervous system
- can also occur independently as autoimmune disorder

Anti-Hu
- associated with small cell lung carcinoma and neuroblastomas
- sensory neuropathy - may be painful
- cerebellar syndrome
- encephalomyelitis

Anti-Yo
- associated with ovarian and breast cancer
- cerebellar syndrome

Anti-GAD antibody
- associated with breast, colorectal and small cell lung carcinoma
- stiff person's syndrome or diffuse hypertonia

Anti-Ri
- associated with breast and small cell lung carcinoma
- ocular opsoclonus-myoclonus

Purkinje cell antibody
- peripheral neuropathy in breast cancer

# NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome is a rare but dangerous condition seen in patients taking antipsychotic medication. It carries a mortality of up to 10% and can also occur with atypical antipsychotics. It may also occur with dopaminergic drugs (such as levodopa) for Parkinson's disease, usually when the drug is suddenly stopped or the dose reduced.

The pathophysiology is unknown but one theory is that the dopamine blockade induced by antipsychotics triggers massive glutamate release and subsequent neurotoxicity and muscle damage.

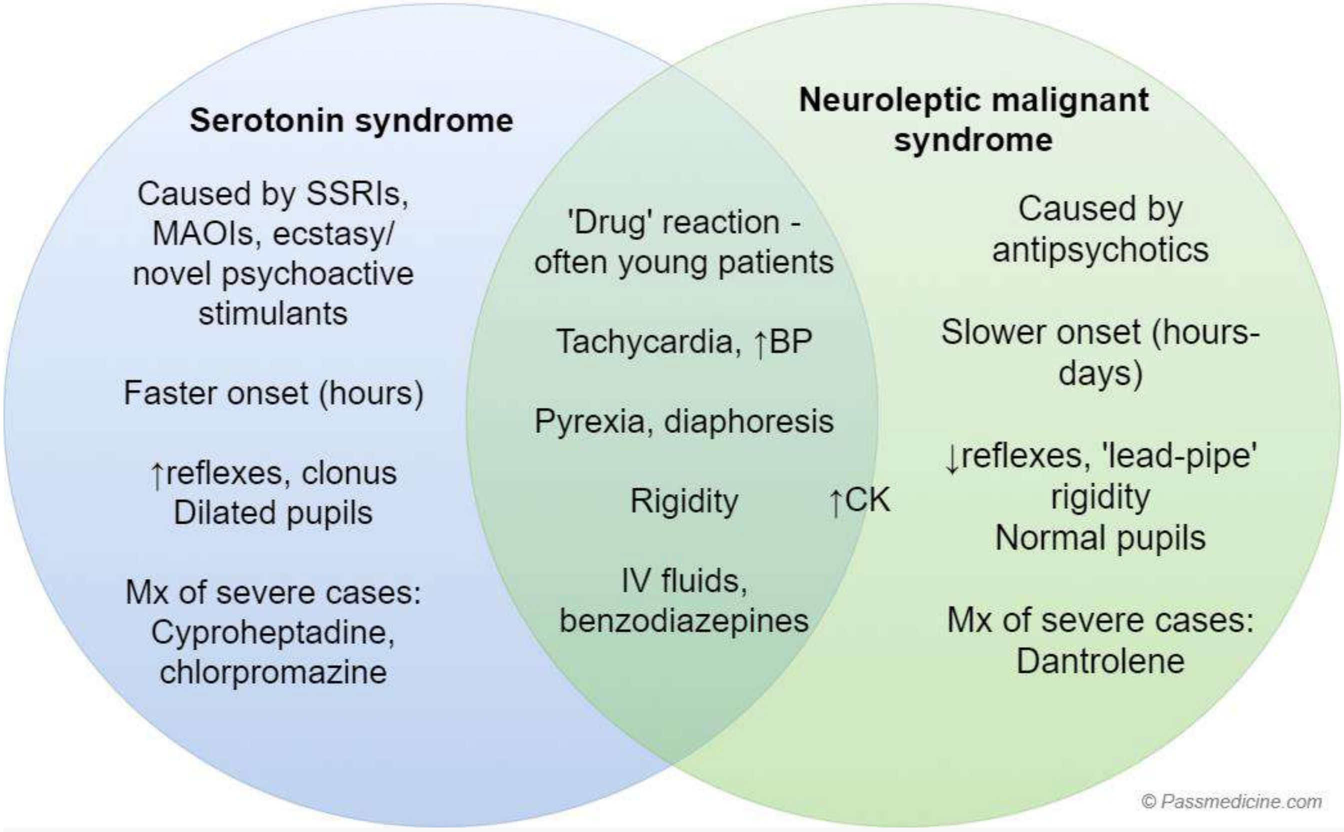
It occurs within hours to days of starting an antipsychotic (antipsychotics are also known as neuroleptics, hence the name) and the typical features are:

- pyrexia
- muscle rigidity
- autonomic lability: typical features include hypertension, tachycardia and tachypnoea
- agitated delirium with confusion

A raised creatine kinase is present in most cases. Acute kidney injury (secondary to rhabdomyolysis) may develop in severe cases. A leukocytosis may also be seen

Management

- stop antipsychotic
- patients should be transferred to a medical ward if they are on a psychiatric ward and often they are nursed in intensive care units
- IV fluids to prevent renal failure
- dantrolene may be useful in selected cases
- thought to work by decreasing excitation-contraction coupling in skeletal muscle by binding to the ryanodine receptor, and decreasing the release of calcium from the sarcoplasmic reticulum
- bromocriptine, dopamine agonist, may also be used


Serotonin syndrome
Caused by SSRIs, MAOIs, ecstasy/ novel psychoactive stimulants
Faster onset (hours)
↑reflexes, clonus
Dilated pupils
Mx of severe cases: Cyproheptadine, chlorpromazine
Neuroleptic malignant syndrome
Caused by antipsychotics
Slower onset (hours-days)
↓reflexes, 'lead-pipe' rigidity
Normal pupils
Mx of severe cases: Dantrolene
'Drug' reaction - often young patients
Tachycardia, ↑BP
Pyrexia, diaphoresis
Rigidity
↑CK
IV fluids, benzodiazepines
© Passmedicine.com

Venn diagram showing contrasting serotonin syndrome with neuroleptic malignant syndrome. Note that both conditions can cause a raised creatine kinase (CK) but it tends to be more associated with NMS.

# DYSTROPHINOPATHIES

Overview

- X-linked recessive
- due to mutation in the gene encoding dystrophin, dystrophin gene on Xp21
- dystrophin is part of a large membrane associated protein in muscle which connects the muscle membrane to actin, part of the muscle cytoskeleton
- in Duchenne muscular dystrophy there is a frameshift mutation resulting in one or both of the binding sites are lost leading to a severe form
- in Becker muscular dystrophy there is a non-frameshift insertion in the dystrophin gene resulting in both binding sites being preserved leading to a milder form

Duchenne muscular dystrophy

- progressive proximal muscle weakness from 5 years
- calf pseudohypertrophy
- Gower's sign: child uses arms to stand up from a squatted position
- 30% of patients have intellectual impairment

Becker muscular dystrophy

- develops after the age of 10 years
- intellectual impairment much less common

# NEUROMYELITIS OPTICA

Neuromyelitis optica (NMO) is monophasic or relapsing-remitting demyelinating CNS disorder Although previously thought to be a variant of multiple sclerosis, it is now recognised to be a distinct disease, particularly prevalent in Asian populations1. It typically involves the optic nerves and cervical spine, with imaging of the brain frequently normal. Vomiting is also a common presenting complaint.

Diagnosis is requires bilateral optic neuritis, myelitis and 2 of the follow 3 criteria2:
1. Spinal cord lesion involving 3 or more spinal levels
2. Initially normal MRI brain
3. Aquaporin 4 positive serum antibody

1. Wingerchuk DM, Lennon VA, Lucchinetti CF et al. The spectrum of neuromyelitis optica. Lancet Neurol. 2007;6(9):805.

2. Wingerchuk DM, Lennon VA, Pittock SJ et al. Revised diagnostic criteria for neuromyelitis optica. Neurology. 2006;66(10):1485.

# NORMAL PRESSURE HYDROCEPHALUS

Normal pressure hydrocephalus is a reversible cause of dementia seen in elderly patients. It is thought to be secondary to reduced CSF absorption at the arachnoid villi. These changes may be secondary to head injury, subarachnoid haemorrhage or meningitis.

A classical triad of features is seen

- urinary incontinence
- dementia and bradyphrenia
- gait abnormality (may be similar to Parkinson's disease)

It is thought around 60% of patients will have all 3 features at the time of diagnosis. Symptoms typically develop over a few months.

Imaging

- hydrocephalus with an enlarged fourth ventricle
- in addition to the ventriculomegaly there is typically an absence of substantial sulcal atrophy

Management

- ventriculoperitoneal shunting
- around 10% of patients who have shunts experience significant complications such as seizures, infection and intracerebral haemorrhages

# PARKINSON'S DISEASE: FEATURES

Parkinson's disease is a progressive neurodegenerative condition caused by degeneration of dopaminergic neurons in the substantia nigra. This results in a classic triad of features: bradykinesia, tremor and rigidity. The symptoms of Parkinson's disease are characteristically asymmetrical.

Epidemiology
- around twice as common in men
- mean age of diagnosis is 65 years

Bradykinesia
- poverty of movement also seen, sometimes referred to as hypokinesia
- short, shuffling steps with reduced arm swinging
- difficulty in initiating movement

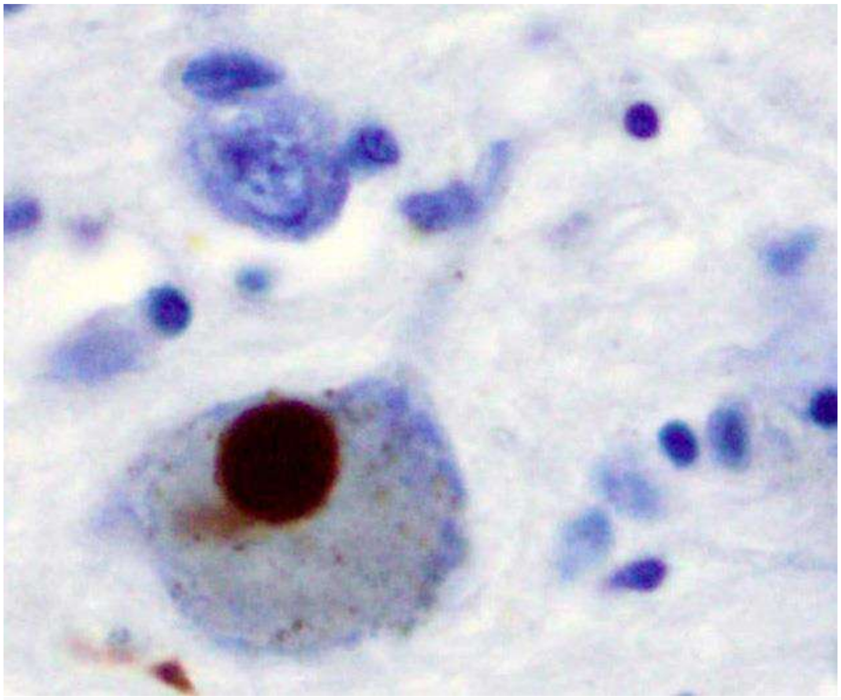
Tremor
- most marked at rest, 3-5 Hz
- worse when stressed or tired, improves with voluntary movement
- typically 'pill-rolling', i.e. in the thumb and index finger

Rigidity
- lead pipe
- cogwheel: due to superimposed tremor

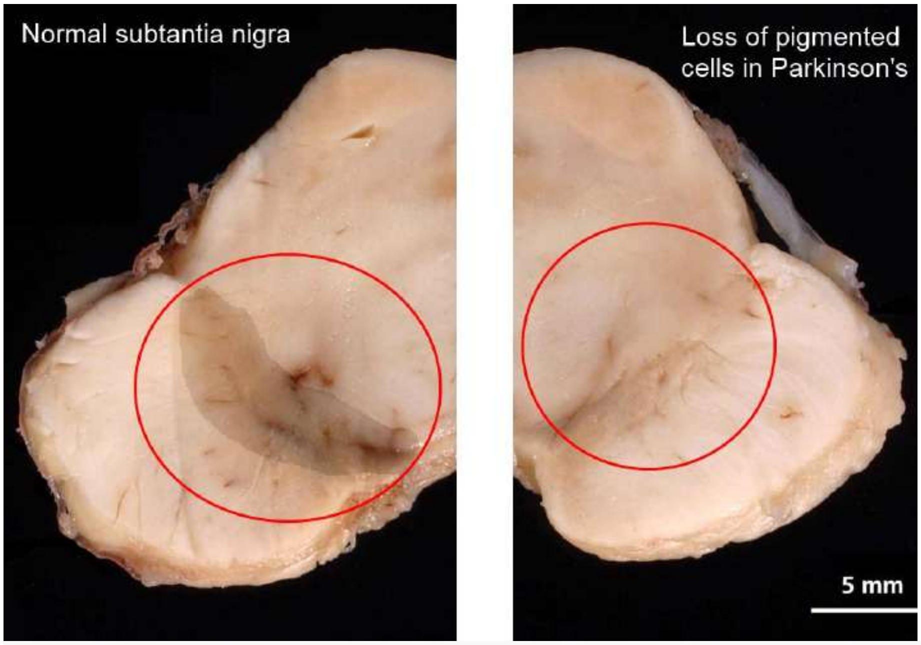
Other characteristic features
- mask-like facies
- flexed posture
- micrographia
- drooling of saliva
- psychiatric features: depression is the most common feature (affects about 40%); dementia, psychosis and sleep disturbances may also occur
- impaired olfaction
- REM sleep behaviour disorder
- fatigue
- autonomic dysfunction:
- postural hypotension

**Drug-induced parkinsonism** has slightly different features to Parkinson's disease:
- motor symptoms are generally rapid onset and bilateral
- rigidity and rest tremor are uncommon

Diagnosis is usually clinical. However, if there is difficulty differentiating between essential tremor and Parkinson's disease NICE recommend considering 123I-FP-CIT single photon emission computed tomography (SPECT).



A Lewy body (stained brown) in a brain cell of the substantia nigra in Parkinson's disease. The brown colour is positive immunohistochemistry staining for alpha-synuclein.


Normal subtantia nigra
Loss of pigmented cells in Parkinson's
5 mm

Discoloration of the substantia nigra due to loss of pigmented nerve cells.

## PARKINSON'S DISEASE: MANAGEMENT

Parkinsons disease should only be diagnosed, and management initiated, by a specialist with expertise in movement disorders. However, it is important for all doctors to be aware of the medications used in Parkinson's given the prevalence of this condition. NICE published guidelines in 2017 regarding the management of Parkinson's disease.

For first-line treatment:

- if the motor symptoms are affecting the patient's quality of life: levodopa
- if the motor symptoms are not affecting the patient's quality of life: dopamine agonist (non-ergot derived), levodopa or monoamine oxidase B (MAO-B) inhibitor

Whilst all drugs used to treat Parkinson's can cause a wide variety of side-effects NICE produced tables to help with decision making:

| | **Levodopa** | **Dopamine agonists** | **MAO-B inhibitors** |
|---|---|---|---|
| **Motor symptoms** | More improvement in motor symptoms | Less improvement in motor symptoms | Less improvement in motor symptoms |
| **Activities of daily living** | More improvement in activities of daily living | Less improvement in activities of daily living | Less improvement in activities of daily living |
| **Motor complications** | More motor complications | Fewer motor complications | Fewer motor complications |
| **Adverse events** | Fewer specified adverse events* | More specified adverse events* | Fewer specified adverse events* |

* excessive sleepiness, hallucinations and impulse control disorders

If a patient continues to have symptoms despite optimal levodopa treatment or has developed dyskinesia then NICE recommend the addition of a dopamine agonist, MAO-B inhibitor or catechol-O-methyl transferase (COMT) inhibitor as an adjunct. Again, NICE summarise the main points in terms of decision making:

| | **Dopamine agonists** | **MAO-B inhibitors** | **COMT inhibitors** | **Amantadine** |
|---|---|---|---|---|
| **Motor symptoms** | Improvement in motor symptoms | Improvement in motor symptoms | Improvement in motor symptoms | No evidence of improvement in motor symptoms |
| **Activities of daily living** | Improvement in activities of daily living | Improvement in activities of daily living | Improvement in activities of daily living | No evidence of improvement in activities of daily living |
| **Off time** | More off-time reduction | Off-time reduction | Off-time reduction | No studies reporting this outcome |
| **Adverse events** | Intermediate risk of adverse events | Fewer adverse events | More adverse events | No studies reporting this outcome |

| | Dopamine agonists | MAO-B inhibitors | COMT inhibitors | Amantadine |
|---|---|---|---|---|
| **Hallucinations** | More risk of hallucinations | Lower risk of hallucinations | Lower risk of hallucinations | No studies reporting this outcome |

**Specific points regarding Parkinson's medication**

NICE reminds us of the risk of acute akinesia or neuroleptic malignant syndrome if medication is not taken/absorbed (for example due to gastroenteritis) and advise against giving patients a 'drug holiday' for the same reason.

- Impulse control disorders have become a significant issue in recent years. These can occur with any dopaminergic therapy but are more common with:
- dopamine agonist therapy
- a history of previous impulsive behaviours
- a history of alcohol consumption and/or smoking

If excessive daytime sleepiness develops then patients should not drive. Medication should be adjusted to control symptoms. Modafinil can be considered if alternative strategies fail.

If orthostatic hypotension develops then a medication review looking at potential causes should be done. If symptoms persist then midodrine (acts on peripheral alpha-adrenergic receptors to increase arterial resistance) can be considered.

Consider glycopyrronium bromide to manage drooling of saliva in people with Parkinson's disease.

**Further information regarding specific anti-Parkinson's medication**

Levodopa

- usually combined with a decarboxylase inhibitor (e.g. carbidopa or benserazide) to prevent peripheral metabolism of levodopa to dopamine
- reduced effectiveness with time (usually by 2 years)
- unwanted effects: dyskinesia (involuntary writhing movements), 'on-off' effect, dry mouth, anorexia, palpitations, postural hypotension, psychosis, drowsiness
- no use in neuroleptic induced parkinsonism
- it is important not to acutely stop levodopa, for example if a patient is admitted to hospital. If a patient with Parkinson's disease cannot take levodopa orally, they can be given a dopamine agonist patch as rescue medication to prevent acute dystonia

Dopamine receptor agonists

- e.g. bromocriptine, ropinirole, cabergoline, apomorphine
- ergot-derived dopamine receptor agonists (bromocriptine, cabergoline) have been associated with pulmonary, retroperitoneal and cardiac fibrosis. The Committee on Safety of Medicines

advice that an echocardiogram, ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored

- patients should be warned about the potential for dopamine receptor agonists to cause impulse control disorders and excessive daytime somnolence
- more likely than levodopa to cause hallucinations in older patients. Nasal congestion and postural hypotension are also seen in some patients

MAO-B (Monoamine Oxidase-B) inhibitors

- e.g. selegiline
- inhibits the breakdown of dopamine secreted by the dopaminergic neurons

Amantadine

- mechanism is not fully understood, probably increases dopamine release and inhibits its uptake at dopaminergic synapses
- side-effects include ataxia, slurred speech, confusion, dizziness and livedo reticularis

COMT (Catechol-O-Methyl Transferase) inhibitors

- e.g. entacapone, tolcapone
- COMT is an enzyme involved in the breakdown of dopamine, and hence may be used as an adjunct to levodopa therapy
- used in conjunction with levodopa in patients with established PD

Antimuscarinics

- block cholinergic receptors
- now used more to treat drug-induced parkinsonism rather than idiopathic Parkinson's disease
- help tremor and rigidity
- e.g. procyclidine, benzotropine, trihexyphenidyl (benzhexol)

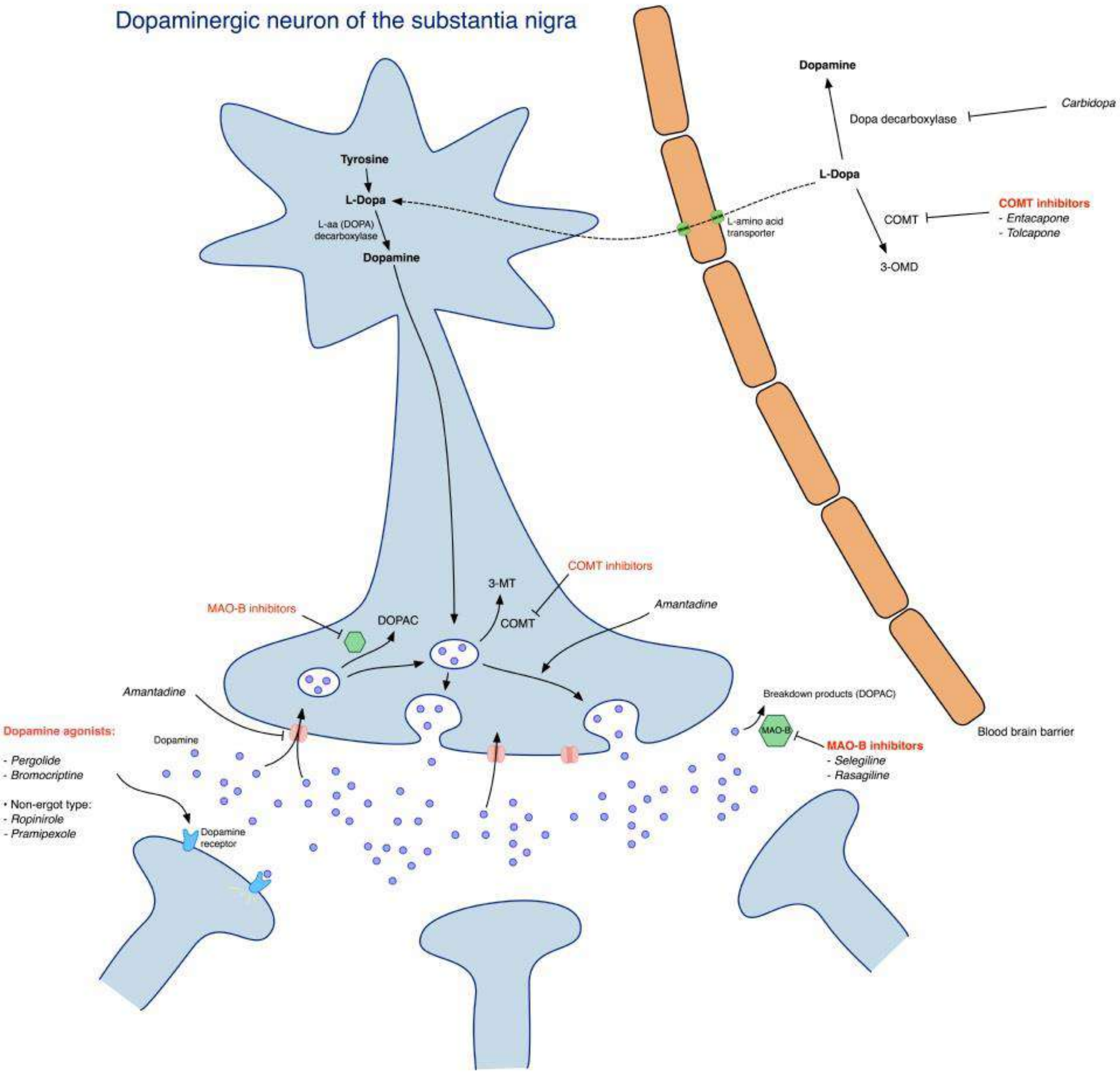

Dopaminergic neuron of the substantia nigra
Dopamine
Dopa decarboxylase
Carbidopa
L-Dopa
COMT
COMT inhibitors
- Entacapone
- Tolcapone
3-OMD
L-amino acid transporter
Tyrosine
L-Dopa
L-aa (DOPA) decarboxylase
Dopamine
COMT inhibitors
3-MT
COMT
MAO-B inhibitors
DOPAC
Amantadine
Amantadine
Dopamine agonists:
- Pergolide
- Bromocriptine
• Non-ergot type:
- Ropinirole
- Pramipexole
Dopamine
Dopamine receptor
Breakdown products (DOPAC)
MAO-B
MAO-B inhibitors
- Selegiline
- Rasagiline
Blood brain barrier

Diagram showing the mechanism of action of Parkinson's drugs

# LEVODOPA

Overview

- usually combined with a decarboxylase inhibitor (e.g. carbidopa or benserazide) to prevent peripheral metabolism of L-dopa to dopamine
- reduced effectiveness with time (usually by 2 years)
- no use in neuroleptic induced parkinsonism

Adverse effects
- dyskinesia
- 'on-off' effect
- postural hypotension
- cardiac arrhythmias
- nausea & vomiting
- psychosis
- reddish discolouration of urine upon standing

# PARKINSONISM

Causes of Parkinsonism
- Parkinson's disease
- drug-induced e.g. antipsychotics, metoclopramide*
- progressive supranuclear palsy
- multiple system atrophy
- Wilson's disease
- post-encephalitis
- dementia pugilistica (secondary to chronic head trauma e.g. boxing)
- toxins: carbon monoxide, MPTP

*Domperidone does not cross the blood-brain barrier and therefore does not cause extra-pyramidal side-effects.

# ESSENTIAL TREMOR

Essential tremor (previously called benign essential tremor) is an autosomal dominant condition which usually affects both upper limbs

Features
- postural tremor: worse if arms outstretched
- improved by alcohol and rest
- most common cause of titubation (head tremor)

Management
- propranolol is first-line
- primidone is sometimes used

# PERIPHERAL NEUROPATHY

Peripheral neuropathy may be divided into conditions which predominately cause a motor or sensory loss

Predominately motor loss
- Guillain-Barre syndrome
- porphyria
- lead poisoning
- hereditary sensorimotor neuropathies (HSMN) - Charcot-Marie-Tooth
- chronic inflammatory demyelinating polyneuropathy (CIDP)
- diphtheria

Predominately sensory loss
- diabetes
- uraemia
- leprosy
- alcoholism
- vitamin B12 deficiency
- amyloidosis

Alcoholic neuropathy
- secondary to both direct toxic effects and reduced absorption of B vitamins
- sensory symptoms typically present prior to motor symptoms

Vitamin B12 deficiency
- subacute combined degeneration of spinal cord
- dorsal column usually affected first (joint position, vibration) prior to distal paraesthesia

# DRUGS CAUSING PERIPHERAL NEUROPATHY

Drugs causing a peripheral neuropathy
- amiodarone
- isoniazid
- vincristine
- nitrofurantoin
- metronidazole

# PERIPHERAL NEUROPATHY: DEMYELINATING VS. AXONAL

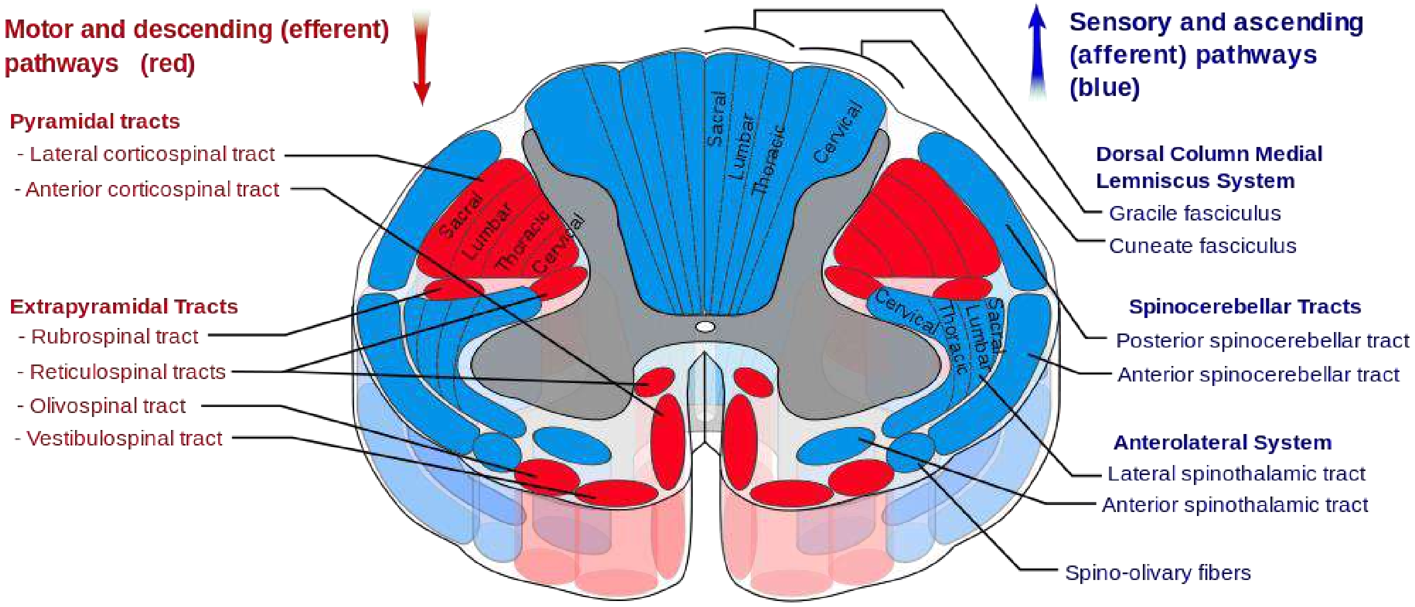
Demyelinating pathology
- Guillain-Barre syndrome
- chronic inflammatory demyelinating polyneuropathy (CIDP)
- amiodarone
- hereditary sensorimotor neuropathies (HSMN) type I
- paraprotein neuropathy

Axonal pathology
- alcohol
- diabetes mellitus*
- vasculitis
- vitamin B12 deficiency*
- hereditary sensorimotor neuropathies (HSMN) type II

* may also cause a demyelinating picture

# SPINAL CORD LESIONS

The diagram belows shows cross-section view of the spinal cord:


Motor and descending (efferent) pathways (red)
Pyramidal tracts
- Lateral corticospinal tract
- Anterior corticospinal tract
Extrapyramidal Tracts
- Rubrospinal tract
- Reticulospinal tracts
- Olivospinal tract
- Vestibulospinal tract
Sacral
Lumbar
Thoracic
Cervical
Sensory and ascending (afferent) pathways (blue)
Dorsal Column Medial Lemniscus System
Gracile fasciculus
Cuneate fasciculus
Spinocerebellar Tracts
Posterior spinocerebellar tract
Anterior spinocerebellar tract
Anterolateral System
Lateral spinothalamic tract
Anterior spinothalamic tract
Spino-olivary fibers

### Motor lesions

Amyotrophic lateral sclerosis (motor neuron disease)

- affects both upper (corticospinal tracts) and lower motor neurons
- results in a combination of upper and lower motor neuron signs

Poliomyelitis

- affects anterior horns resulting in lower motor neuron signs

### Combined motor and sensory lesions

| Disorder | Tracts affected | Clinical notes |
|---|---|---|
| Brown-Sequard syndrome (spinal cord hemisection) | 1. Lateral corticospinal tract<br>2. Dorsal columns<br>3. Lateral spinothalamic tract | 1. Ipsilateral spastic paresis below lesion<br>2. Ipsilateral loss of proprioception and vibration sensation<br>3. Contralateral loss of pain and temperature sensation |
| Subacute combined degeneration of the spinal cord (vitamin B12 & E deficiency) | 1. Lateral corticospinal tracts<br>2. Dorsal columns<br>3. Spinocerebellar tracts | 1. Bilateral spastic paresis<br>2. Bilateral loss of proprioception and vibration sensation<br>3. Bilateral limb ataxia |

| Disorder | Tracts affected | Clinical notes |
|---|---|---|
| Friedrich's ataxia | Same as subacute combined degeneration of the spinal cord (see above) | Same as subacute combined degeneration of the spinal cord (see above)<br>In addition cerebellar ataxia → other features e.g. intention tremor |
| Anterior spinal artery occlusion | 1. Lateral corticospinal tracts<br>2. Lateral spinothalamic tracts | 1. Bilateral spastic paresis<br>2. Bilateral loss of pain and temperature sensation |
| Syringomyelia | 1. Ventral horns<br>2. Lateral spinothalamic tract | 1. Flacid paresis (typically affecting the intrinsic hand muscles)<br>2. Loss of pain and temperature sensation |
| Multiple sclerosis | Asymmetrical, varying spinal tracts involved | Combination of motor, sensory and ataxia symptoms |

**Sensory lesions**

| Disorder | Tracts affected | Clinical notes |
|---|---|---|
| Neurosyphilis (tabes dorsalis) | 1. Dorsal columns | 1. Loss of proprioception and vibration sensation |

# DEGENERATIVE CERVICAL MYELOPATHY

Degenerative cervical myelopathy (DCM) has a number of risk factors, which include smoking due to its effects on the intervertebral discs, genetics and occupation - those exposing patients to high axial loading [1].

The presentation of DCM is very variable. Early symptoms are often subtle and can vary in severity day to day, making the disease difficult to detect initially. However as a progressive condition, worsening, deteriorating or new symptoms should be a warning sign.

DCM symptoms can include any combination of [1]:

- Pain (affecting the neck, upper or lower limbs)
- Loss of motor function (loss of digital dexterity, preventing simple tasks such as holding a fork or doing up their shirt buttons, arm or leg weakness/stiffness leading to impaired gait and imbalance
- Loss of sensory function causing numbness
- Loss of autonomic function (urinary or faecal incontinence and/or impotence) - these can occur and do not necessarily suggest cauda equina syndrome in the absence of other hallmarks of that condition

- Hoffman's sign: is a reflex test to assess for cervical myelopathy. It is performed by gently flicking one finger on a patient's hand. A positive test results in reflex twitching of the other fingers on the same hand in response to the flick.

The most common symptoms at presentation of DCM are unknown, but in one series 50% of patients were initially incorrectly diagnosed and sometimes treated for carpal tunnel syndrome [2].

An MRI of the cervical spine is the gold standard test where cervical myelopathy is suspected. It may reveal disc degeneration and ligament hypertrophy, with accompanying cord signal change.

All patients with degenerative cervical myelopathy should be urgently referred for assessment by specialist spinal services (neurosurgery or orthopaedic spinal surgery). This is due to the importance of early treatment. The timing of surgery is important, as any existing spinal cord damage can be permanent. Early treatment (within 6 months of diagnosis) offers the best chance of a full recovery but at present, most patients are presenting too late. In one study, patients averaged over 5 appointments before diagnosis, representing >2 years.

Currently, decompressive surgery is the only effective treatment. It has been shown to prevent disease progression. Close observation is an option for mild stable disease, but anything progressive or more severe requires surgery to prevent further deterioration. Physiotherapy should only be initiated by specialist services, as manipulation can cause more spinal cord damage.

References
1. Baron EM, Young WF. Cervical spondylotic myelopathy: a brief review of its pathophysiology, clinical course, and diagnosis. Neurosurgery. 2007 Jan;60(1 Supp1 1):S35-41.
2. Behrbalk E, Salame K, Regev GJ, Keynan O, Boszczyk B, Lidar Z. Delayed diagnosis of cervical spondylotic myelopathy by primary care physicians. Neurosurg Focus. 2013 Jul;35(1):E1.

# SUBACUTE COMBINED DEGENERATION OF SPINAL CORD

Basics

- due to vitamin B12 deficiency
- dorsal + lateral columns affected
- joint position and vibration sense lost first then distal paraesthesia
- upper motor neuron signs typically develop in the legs, classically extensor plantars, brisk knee reflexes, absent ankle jerks
- if untreated stiffness and weakness persist

# STROKE BY ANATOMY

| Site of the lesion | Associated effects |
|---|---|
| Anterior cerebral artery | Contralateral hemiparesis and sensory loss, lower extremity > upper |
| Middle cerebral artery | Contralateral hemiparesis and sensory loss, upper extremity > lower<br>Contralateral homonymous hemianopia<br>Aphasia |
| Posterior cerebral artery | Contralateral homonymous hemianopia with macular sparing<br>Visual agnosia |
| Weber's syndrome (branches of the posterior cerebral artery that supply the midbrain) | Ipsilateral CN III palsy<br>Contralateral weakness of upper and lower extremity |
| Posterior inferior cerebellar artery (lateral medullary syndrome, Wallenberg syndrome) | Ipsilateral: facial pain and temperature loss<br>Contralateral: limb/torso pain and temperature loss<br>Ataxia, nystagmus |
| Anterior inferior cerebellar artery (lateral pontine syndrome) | Symptoms are similar to Wallenberg's (see above), but:<br>Ipsilateral: facial paralysis and deafness |
| Retinal/ophthalmic artery | Amaurosis fugax |
| Basilar artery | 'Locked-in' syndrome |

Lacunar strokes
- present with either isolated hemiparesis, hemisensory loss or hemiparesis with limb ataxia
- strong association with hypertension
- common sites include the basal ganglia, thalamus and internal capsule

# STROKE: TYPES

The **Oxford Stroke Classification** (also known as the Bamford Classification) classifies strokes based on the initial symptoms. A summary is as follows:

The following criteria should be assessed:
1. unilateral hemiparesis and/or hemisensory loss of the face, arm & leg
2. homonymous hemianopia
3. higher cognitive dysfunction e.g. dysphasia

Total anterior circulation infarcts (TACI, c. 15%)
- involves middle and anterior cerebral arteries
- all 3 of the above criteria are present

Partial anterior circulation infarcts (PACI, c. 25%)

- involves smaller arteries of anterior circulation e.g. upper or lower division of middle cerebral artery
- 2 of the above criteria are present

Lacunar infarcts (LACI, c. 25%)

- involves perforating arteries around the internal capsule, thalamus and basal ganglia
- presents with 1 of the following:
  1. unilateral weakness (and/or sensory deficit) of face and arm, arm and leg or all three.
  2. pure sensory stroke.
  3. ataxic hemiparesis

Posterior circulation infarcts (POCI, c. 25%)

- involves vertebrobasilar arteries
- presents with 1 of the following:
  - cerebellar or brainstem syndromes
  - loss of consciousness
  - isolated homonymous hemianopia

**Other recognised patterns of stroke:**

Lateral medullary syndrome (posterior inferior cerebellar artery)

- aka Wallenberg's syndrome
- ipsilateral: ataxia, nystagmus, dysphagia, facial numbness, cranial nerve palsy e.g. Horner's
- contralateral: limb sensory loss

Weber's syndrome

- ipsilateral III palsy
- contralateral weakness

# STROKE: ASSESSMENT

Whilst the diagnosis of stroke may sometimes be obvious in many cases the presenting symptoms may be vague and accurate assessment difficult.

The FAST screening tool (Face/Arms/Speech/Time) is widely known by the general public following a publicity campaign. It has a positive predictive value of 78%.

A variant of FAST called the ROSIER score is useful for medical professionals. It is validated tool recommended by the Royal College of Physicians.

**ROSIER score**

Exclude hypoglycaemia first, then assess the following:

| **Assessment** | **Scoring** |
|---|---|
| Loss of consciousness or syncope | - 1 point |
| Seizure activity | - 1 point |
| New, acute onset of: | |
| • asymmetric facial weakness | + 1 point |
| • asymmetric arm weakness | + 1 point |
| • asymmetric leg weakness | + 1 point |
| • speech disturbance | + 1 point |
| • visual field defect | + 1 point |

A stroke is likely if > 0.

**Investigations**

A non-contrast CT head scan is the first line radiological investigation for suspected stroke

# STROKE: MANAGEMENT

The Royal College of Physicians (RCP) published guidelines on the diagnosis and management of patients following a stroke in 2004. NICE updated their stroke guidelines in 2019.

Selected points relating to the management of acute stroke include:

- blood glucose, hydration, oxygen saturation and temperature should be maintained within normal limits
- blood pressure should not be lowered in the acute phase unless there are complications e.g. Hypertensive encephalopathy*
- aspirin 300mg orally or rectally should be given as soon as possible if a haemorrhagic stroke has been excluded
- with regards to atrial fibrillation, the RCP state: 'anticoagulants should not be started until brain imaging has excluded haemorrhage, and usually not until 14 days have passed from the onset of an ischaemic stroke'
- if the cholesterol is > 3.5 mmol/l patients should be commenced on a statin. Many physicians will delay treatment until after at least 48 hours due to the risk of haemorrhagic transformation

**Thrombolysis for acute ischaemic stroke**

Thrombolysis with alteplase should only be given if:

- it is administered within 4.5 hours of onset of stroke symptoms (unless as part of a clinical trial)
- haemorrhage has been definitively excluded (i.e. Imaging has been performed)

Contraindications to thrombolysis:

| **Absolute** | **Relative** |
|---|---|
| - Previous intracranial haemorrhage<br>- Seizure at onset of stroke<br>- Intracranial neoplasm<br>- Suspected subarachnoid haemorrhage<br>- Stroke or traumatic brain injury in preceding 3 months<br>- Lumbar puncture in preceding 7 days<br>- Gastrointestinal haemorrhage in preceding 3 weeks<br>- Active bleeding<br>- Pregnancy<br>- Oesophageal varices<br>- Uncontrolled hypertension >200/120mmHg | - Concurrent anticoagulation (INR >1.7)<br>- Haemorrhagic diathesis<br>- Active diabetic haemorrhagic retinopathy<br>- Suspected intracardiac thrombus<br>- Major surgery / trauma in the preceding 2 weeks |

**Thrombectomy for acute ischaemic stroke**

Mechanical thrombectomy is an exciting new treatment option for patients with an acute ischaemic stroke. NICE incorporated recommendations into their 2019 guidelines. It is important to remember the significant resources and senior personnel to provide such a service 24 hours a day. NICE recommend that all decisions about thrombectomy take into account a patient's overall clinical status:

- NICE recommend a pre-stroke functional status of less than 3 on the modified Rankin scale and a score of more than 5 on the National Institutes of Health Stroke Scale (NIHSS)

Offer thrombectomy as soon as possible and within 6 hours of symptom onset, together with intravenous thrombolysis (if within 4.5 hours), to people who have:
acute ischaemic stroke and

- confirmed occlusion of the **proximal anterior circulation** demonstrated by computed tomographic angiography (CTA) or magnetic resonance angiography (MRA)

Offer thrombectomy as soon as possible to people who were last known to be well between 6 hours and 24 hours previously (including wake-up strokes):

- confirmed occlusion of the **proximal anterior circulation** demonstrated by CTA or MRA and
- if there is the potential to salvage brain tissue, as shown by imaging such as CT perfusion or diffusion-weighted MRI sequences showing limited infarct core volume

Consider thrombectomy together with intravenous thrombolysis (if within 4.5 hours) as soon as possible for people last known to be well up to 24 hours previously (including wake-up strokes):

- who have acute ischaemic stroke and confirmed occlusion of the **proximal posterior circulation (that is, basilar or posterior cerebral artery)** demonstrated by CTA or MRA and
- if there is the potential to salvage brain tissue, as shown by imaging such as CT perfusion or diffusion-weighted MRI sequences showing limited infarct core volume

**Secondary prevention**

NICE also published a technology appraisal in 2010 on the use of clopidogrel and dipyridamole

Recommendations from NICE include:

- clopidogrel is now recommended by NICE ahead of combination use of aspirin plus modified-release (MR) dipyridamole in people who have had an ischaemic stroke
- aspirin plus MR dipyridamole is now recommended after an ischaemic stroke only if clopidogrel is contraindicated or not tolerated, but treatment is no longer limited to 2 years' duration
- MR dipyridamole alone is recommended after an ischaemic stroke only if aspirin or clopidogrel are contraindicated or not tolerated, again with no limit on duration of treatment

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST** criteria or > 50% according to NASCET*** criteria

*the 2009 Controlling hypertension and hypotension immediately post-stroke (CHHIPS) trial may change thinking on this but guidelines have yet to change to reflect this
**European Carotid Surgery Trialists' Collaborative Group
***North American Symptomatic Carotid Endarterectomy Trial

## STROKE MANAGEMENT: OTHER ISSUES

This background note focuses on other issues in acute stroke management, particularly management of fluids, glycaemic control, blood pressure management, feeding assessment/management and disability scales.

**Fluid management**

- As in all patients in hospital, regular assessment for fluid status must be undertaken to ensure patients remain normovolaemic
- The NICE guidelines recommend assessing the hydration of all patients with acute stroke on admission, with regular review during their stay
- Greater than 80% of patients who cannot swallow post stroke will recover within 2-4 weeks
- However, it is important to manage fluids in this immediate post-event period as hypovolaemia can worsen the ischaemic penumbra, as well as increase risk of other complications such as infection, deep vein thrombosis, constipation and delirium
- Conversely, over-hydration can also complicate matters by leading to cerebral oedema, cardiac failure and hyponatraemia, therefore it is important to regularly review fluid status in these patients
- Recommendations for management:
- Oral hydration is preferable in all patients who are able to safely swallow

- Intravenous hydration may be necessary otherwise, and although studies have remained contentious regarding choice of intravenous fluid, UptoDate currently recommend isotonic saline without dextrose as the agent of choice in most patients
- Other factors to take into consideration when choosing fluid agent include electrolyte disturbances and/or cardiovascular status

**Glycaemic control**

- It is important to closely monitor and control blood sugar, particularly if they are nil by mouth due to concerns regarding swallowing safety post stroke, and/or in diabetics
- Post stroke, patients with hyperglycaemia have increased mortality independent from their age and the severity of stroke
    - This is likely due to increased tissue acidosis from anaerobic metabolism, free radical generation, and increased blood brain barrier permeability post injury
- The NICE guidelines recommend maintaining a blood sugar level between 4 and 11 mmol/L in people with acute stroke
- Diabetic patients
    - It is important to provide intensive management for diabetics post acute stroke
    - The NICE guidelines suggest optimising insulin treatment using intravenous insulin and glucose infusions
    - Hypoglycaemia also needs to be managed appropriately, as alone it can cause neuronal injury as well as mimic stroke-related neurological deficits

**Blood pressure management**

- Use of anti-hypertensive medications should only be used for blood pressure control in patients post ischaemic stroke if there is a hypertensive emergency with one or more of the following serious concomitant medical issues (according to the NICE guidelines):
- Hypertensive encephalopathy
- Hypertensive nephropathy
- Hypertensive cardiac failure/myocardial infarction
- Aortic dissection
- Pre-eclampsia/eclampsia
- This is because lowering blood pressure too much can potentially compromise collateral blood flow to the affected region, and possibly hasten the time to complete and irreversible tissue infarction
- If treatment is indicated, UptoDate recommend cautious lowering of blood pressure by approximately 15% in the first 24-hours after stroke onset
- UptoDate suggest using intravenous labetalol, nicardipine and clevidipine as first-line agents, due to the possibility for rapid and safe titration to control blood pressure

- However, in patients who are candidates for thrombolytic therapy for acute stroke, blood pressure should be reduced to 185/110mmHg or lower
    - Elevated BP can affect thrombolytic eligibility and delay treatment

  - Timely management of elevated BP is crucial when patients are otherwise eligible for intravenous thrombolysis
  - After thrombolytic therapy, UptoDate recommend ensuring that the blood pressure is stabilised and maintained at or below 180/105mmHg for at least 24 hours after treatment

**Feeding assessment and management**

- All patients presenting with acute stroke must be screened for safe swallowing function prior to further oral intake, as dysphagia is common after stroke
  - This is to reduce the risk of aspiration and subsequent complications
  - This includes prior to any oral intake of food, fluids, and/or medications
- If there are any concerns regarding swallowing, the NICE guidelines recommend specialist assessment of swallowing
  - This should preferably within 24 hours of admission and not greater than 72 hours after
  - Prior to assessment is undertaken, a patient should remain nil by mouth to prevent complications
- Recommendations for patients deemed unsafe for oral intake:
  - Patients should receive nasogastric tube feeding, ideally within 24 hours of admission, unless they have had thrombolytic therapy
  - If nasogastric tube feeding is not tolerated, patients should be considered for a nasal bridle tube/gastrostomy instead
  - Medications need to be assessed to determine if formulations are available for nasogastric feeding, or if conversion to subcutaneous or intravenous forms are required
- Nutritional support may be required for patients at risk of malnutrition post stroke, whether a result from dysphagia, poor oral health or reduced ability to self-feed due to weakness or paralysis

**Disability scales**

- Stroke can result in a number of complications and subsequent disability, therefore disability scales are often used as a measure of functional decline post event and subsequent improvement after medical intervention
- Disability, often measured in terms of functional status (notably, basic activities of daily living), is often the leading cause of morbidity after stroke
- After a patient is medically stabilised after a stroke, they may require transfer to a rehabilitation team for ongoing treatment depending on their level of disability
- Disability is most commonly measured using the Barthel index (BI), an outcome measure for stroke
  - Describes 10 tasks, and is scored according to amount of time or assistance required by the patient for each given task
  - Tasks: feeding, moving from wheelchair to bed, personal toileting, getting on/off toilet, bathing, walking on level surface, ascending/descending stairs, dressing, controlling bowels and controlling bladder
  - The total score is from 0 to 100, with 0 being completely dependent, and 100 being completely independent

- This index should be used to assess the functional status of a patient post stroke, and to monitor their improvement with ongoing rehabilitation to regain independence after the event

# TRANSIENT ISCHAEMIC ATTACK

The original definition of a transient ischaemic attack (TIA) was time-based: a sudden onset of a focal neurologic symptom and/or sign lasting less than 24 hours, brought on by a transient decrease in blood flow. However, this has now changed as it is recognised that even short periods of ischaemia can result in pathological changes to the brain. Therefore, a new 'tissue-based' definition is now used: a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction.

Patients often use the term 'mini-stroke' for TIAs.

**Assessment and referral**
The ABCD2 prognostic score has previously been used to risk stratify patients who present with a suspected TIA. However, data from studies have suggested it performs poorly and it is therefore no longer recommended by NICE Clinical Knowledge Summaries. Instead, NICE recommend:

Immediate antithrombotic therapy:

- give aspirin 300 mg immediately, unless
  - the patient has a bleeding disorder or is taking an anticoagulant (needs immediate admission for imaging to exclude a haemorrhage)
  - the patient is already taking low-dose aspirin regularly: continue the current dose of aspirin until reviewed by a specialist
  - Aspirin is contraindicated: discuss management urgently with the specialist team

If the patient has had more than 1 TIA ('crescendo TIA') or has a suspected cardioembolic source or severe carotid stenosis:

- discuss the need for admission or observation urgently with a stroke specialist

If the patient has had a suspected TIA in the last 7 days:
arrange urgent assessment (within 24 hours) by a specialist stroke physician

If the patient has had a suspected TIA which occurred more than a week previously:
refer for specialist assessment as soon as possible within 7 days

Advise the person not to drive until they have been seen by a specialist.

**Further management**
Antithrombotic therapy

- clopidogrel is recommended first-line (as for patients who've had a stroke)

- aspirin + dipyridamole should be given to patients who cannot tolerate clopidogrel
- these recommendations follow the 2012 Royal College of Physicians National clinical guideline for stroke. Please see the link for more details (section 5.5)
- these guidelines may change following the CHANCE study (NEJM 2013;369:11). This study looked at giving high-risk TIA patients aspirin + clopidogrel for the first 90 days compared to aspirin alone. 11.7% of aspirin only patients had a stroke over 90 days compared to 8.2% of dual antiplatelet patients

With regards to carotid artery endarterectomy:

- recommend if patient has suffered stroke or TIA in the carotid territory and are not severely disabled
- should only be considered if carotid stenosis > 70% according ECST* criteria or > 50% according to NASCET** criteria

*European Carotid Surgery Trialists' Collaborative Group

**North American Symptomatic Carotid Endarterectomy Trial

# SYRINGOMYELIA

Syringomyelia (‘syrinx’ for short) describes a collection of cerebrospinal fluid within the spinal cord.

Syringobulbia is a similar phenomenon in which there is a fluid-filled cavity within the medulla of the brainstem. This is often an extension of the syringomyelia but in rare cases can be an isolated finding.

Causes include:

- a Chiari malformation: strong association
- trauma
- tumours
- idiopathic

The classical presentation of a syrinx is a patient who has a ‘cape-like’ (neck and arms) loss of sensation to temperature but preservation of light touch, proprioception and vibration. Classic examples are of patients who accidentally burn their hands without realising. This is due to the crossing spinothalamic tracts in the anterior commissure of the spinal cord being the first tracts to be affected. Other symptoms and signs include spastic weakness (predominantly of the upper limbs), paraesthesia, neuropathic pain, upgoing plantars and bowel and bladder dysfunction. Scoliosis will occur over a matter of years if the syrinx is not treated. It may cause a Horner’s syndrome due to compression of the sympathetic chain, but this is rare.

Investigation requires a full spine MRI with contrast to exclude a tumour or tethered cord. A brain MRI is also needed to exclude a Chiari malformation.

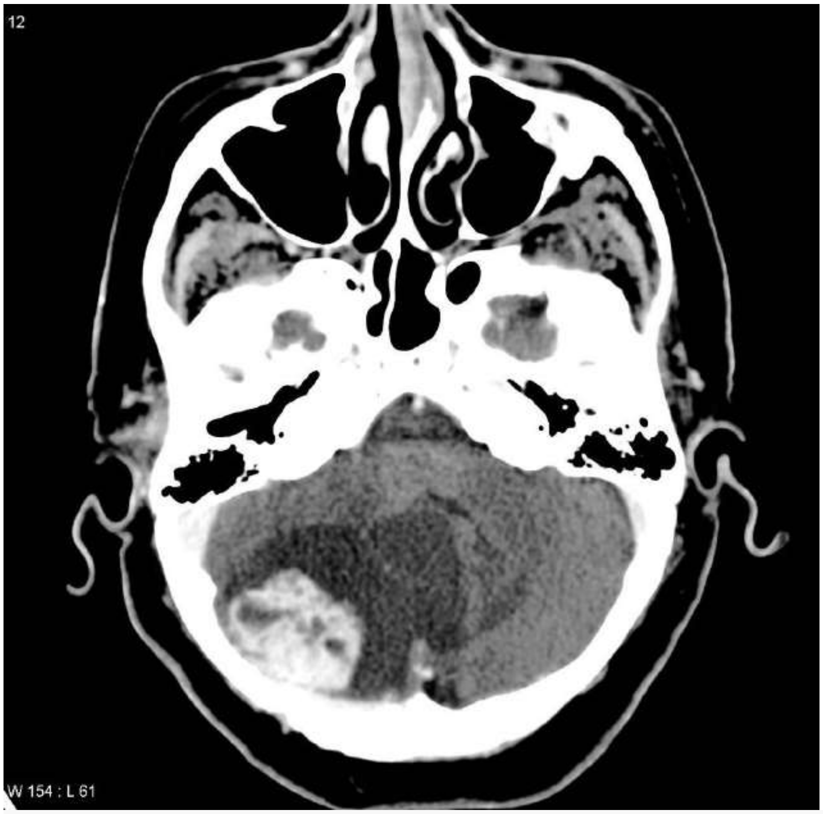
Treatment will be directed at treating the cause of the syrinx. In patients with a persistent or symptomatic syrinx, a shunt into the syrinx can be placed.

# VON HIPPEL-LINDAU SYNDROME

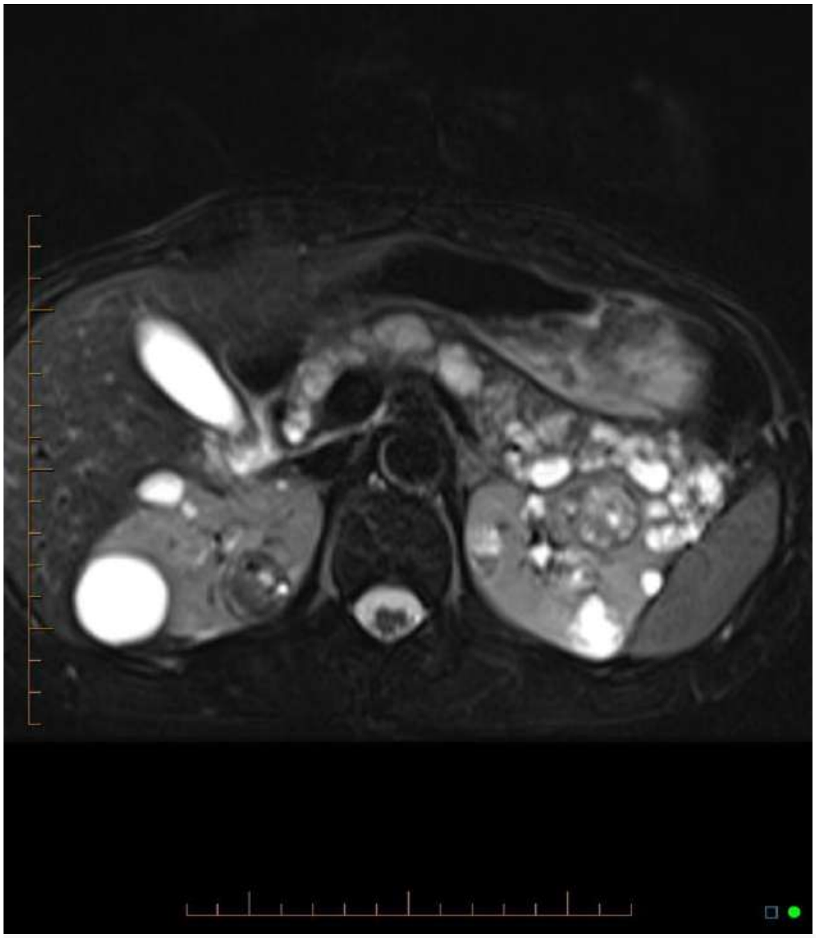
Von Hippel-Lindau (VHL) syndrome is an autosomal dominant condition predisposing to neoplasia. It is due to an abnormality in the VHL gene located on short arm of chromosome 3

Features

- cerebellar haemangiomas: these can cause subarachnoid haemorrhages
- retinal haemangiomas: vitreous haemorrhage
- renal cysts (premalignant)
- phaeochromocytoma
- extra-renal cysts: epididymal, pancreatic, hepatic
- endolymphatic sac tumours
- clear-cell renal cell carcinoma



CT scan showing a cerebellar haemangioma in a patient with Von Hippel-Lindau syndrome.



MRI showing renal cysts in patient with known Von Hippel-Lindau syndrome.

# WERNICKE'S ENCEPHALOPATHY

Wernicke's encephalopathy is a neuropsychiatric disorder caused by thiamine deficiency which is most commonly seen in alcoholics. Rarer causes include: persistent vomiting, stomach cancer, dietary deficiency. A classic triad of ophthalmoplegia/nystagmus, ataxia and confusion may occur. In Wernicke's encephalopathy petechial haemorrhages occur in a variety of structures in the brain including the mamillary bodies and ventricle walls

Features

- nystagmus (the most common ocular sign)
- ophthalmoplegia
- ataxia
- confusion, altered GCS
- peripheral sensory neuropathy

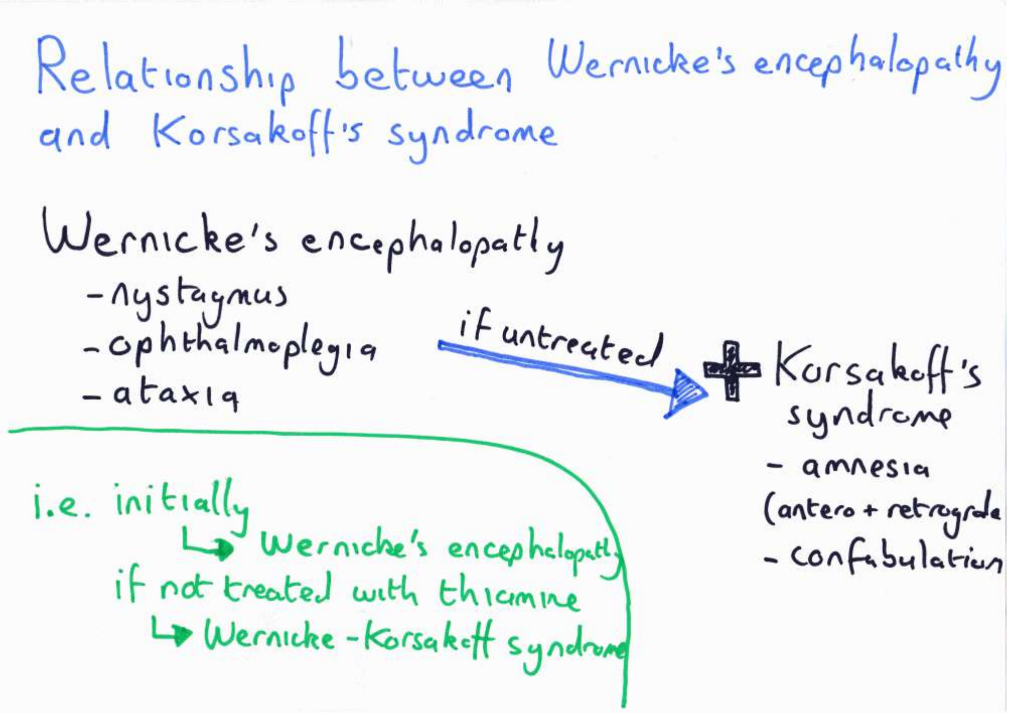
Investigations

- decreased red cell transketolase
- MRI

Treatment is with urgent replacement of thiamine

**Relationship with Korsakoff syndrome**

If not treated Korsakoff's syndrome may develop as well. This is termed Wernicke-Korsakoff syndrome and is characterised by the addition of antero- and retrograde amnesia and confabulation in addition to the above symptoms.


Relationship between Wernicke's encephalopathy and Korsakoff's syndrome
Wernicke's encephalopathy
- nystagmus
- ophthalmoplegia
- ataxia
if untreated
+ Korsakoff's syndrome
- amnesia (antero + retrograde
- confabulation
i.e. initially
Wernicke's encephalopathy
if not treated with thiamine
Wernicke-Korsakoff syndrome

# CEREBELLAR SYNDROME

Unilateral cerebellar lesions cause ipsilateral signs.

Useful and well-known mnemonic to remember symptoms of cerebellar disease is DANISH:
- D - Dysdiadochokinesia, Dysmetria (past-pointing), patients may appear 'Drunk'
- A - Ataxia (limb, truncal)
- N - Nystamus (horizontal = ipsilateral hemisphere)
- I - Intention tremour
- S - Slurred staccato speech, Scanning dysarthria
- H - Hypotonia

Causes
- Friedreich's ataxia, ataxic telangiectasia
- neoplastic: cerebellar haemangioma
- stroke
- alcohol
- multiple sclerosis
- hypothyroidism
- drugs: phenytoin, lead poisoning
- paraneoplastic e.g. secondary to lung cancer

# BROWN-SEQUARD SYNDROME

Overview
- caused by lateral hemisection of the spinal cord

Features
- ipsilateral weakness below lesion
- ipsilateral loss of proprioception and vibration sensation
- contralateral loss of pain and temperature sensation

# ARNOLD-CHIARI MALFORMATION

Arnold-Chiari malformation describes the downward displacement, or herniation, of the cerebellar tonsils through the foramen magnum. Malformations may be congenital or acquired through trauma.

Features

- non-communicating hydrocephalus may develop as a result of obstruction of cerebrospinal fluid (CSF) outflow
- headache
- syringomyelia

## CERVICAL SPONDYLITIC MYELOPATHY

Cervical spondylosis is a degenerative condition affecting the cervical spine, essentially osteoarthritis of the cervical vertebral bodies. If the spinal canal is narrowed due to this process it can press on the spinal cord resulting in neurological dysfunction. Myelopathy is thought to occur in around 5-10% of patients who have cervical spondylosis.

Features
- a variety of motor weakness, sensory loss and bladder/bowel dysfunction may be seen
- neck pain
- wide-based, ataxic or spastic gait
- upper motor neuron weakness in the lower legs - increased reflexes, increased tone and upgoing plantars
- bladder dysfunction e.g. urgency, retention

## CHARCOT-MARIE-TOOTH DISEASE

Charcot-Marie-Tooth Disease is the most common hereditary peripheral neuropathy. It results in a predominantly motor loss. There is no cure, and management is focused on physical and occupational therapy.

Features:
- There may be a history of frequently sprained ankles
- Foot drop
- High-arched feet (pes cavus)
- Hammer toes
- Distal muscle weakness
- Distal muscle atrophy
- Hyporeflexia
- Stork leg deformity

## HSMN

Hereditary sensorimotor neuropathy (HSMN) is a relatively new term which encompasses Charcot-Marie-Tooth disease (also known as peroneal muscular atrophy). Over 7 types have been characterised - however only 2 are common to clinical practice

- HSMN type I: primarily due to demyelinating pathology
- HSMN type II: primarily due to axonal pathology

HSMN type I

- autosomal dominant
- due to defect in PMP-22 gene (which codes for myelin)
- features often start at puberty
- motor symptoms predominate
- distal muscle wasting, pes cavus, clawed toes
- foot drop, leg weakness often first features

# PITUITARY APOPLEXY

Sudden enlargement of pituitary tumour secondary to haemorrhage or infarction.

Features

- sudden onset headache similar to that seen in subarachnoid haemorrhage
- vomiting
- neck stiffness
- visual field defects: classically bitemporal superior quadrantic defect
- extraocular nerve palsies
- features of pituitary insufficiency e.g. Hypotension secondary to hypoadrenalism

# PROGRESSIVE SUPRANUCLEAR PALSY

Overview

- aka Steele-Richardson-Olszewski syndrome
- a 'Parkinson Plus' syndrome

Features

- impairment of vertical gaze (down gaze worse than up gaze - patients may complain of difficultly reading or descending stairs)
- parkinsonism
- falls
- slurring of speech
- cognitive impairment

Management
- poor response to L-dopa

# RESTLESS LEGS SYNDROME

Restless legs syndrome (RLS) is a syndrome of spontaneous, continuous lower limb movements that may be associated with paraesthesia. It is extremely common, affecting between 2-10% of the general population. Males and females are equally affected and a family history may be present

Clinical features
- uncontrollable urge to move legs (akathisia). Symptoms initially occur at night but as condition progresses may occur during the day. Symptoms are worse at rest
- paraesthesias e.g. 'crawling' or 'throbbing' sensations
- movements during sleep may be noted by the partner - periodic limb movements of sleeps (PLMS)

Causes and associations
- there is a positive family history in 50% of patients with idiopathic RLS
- iron deficiency anaemia
- uraemia
- diabetes mellitus
- pregnancy

The diagnosis is clinical although bloods such as ferritin to exclude iron deficiency anaemia may be appropriate

Management
- simple measures: walking, stretching, massaging affected limbs
- treat any iron deficiency
- dopamine agonists are first-line treatment (e.g. Pramipexole, ropinirole)
- benzodiazepines
- gabapentin

# REYE'S SYNDROME

Reye's syndrome is a severe, progressive encephalopathy affecting children that is accompanied by fatty infiltration of the liver, kidneys and pancreas. The aetiology of Reye's syndrome is not fully understood although there is a known association with aspirin use and a viral cause has been postulated

The peak incidence is 2 years of age, features include:

- there may be a history of preceding viral illness
- encephalopathy: confusion, seizures, cerebral oedema, coma
- fatty infiltration of the liver, kidneys and pancreas
- hypoglycaemia

Management is supportive

Although the prognosis has improved over recent years there is still a mortality rate of 15-25%.

# TRANSIENT GLOBAL AMNESIA

Overview

- presents with transient loss of memory function
- patients may appear anxious and repeatedly ask the same question
- patients have no recall of events after the attack
- aetiology is unknown, thought to be due to transient ischaemia to the thalamus (in particular the amygdala and hippocampus)

# GINGIVAL HYPERPLASIA

Drug causes of gingival hyperplasia

- phenytoin
- ciclosporin
- calcium channel blockers (especially nifedipine)

Other causes of gingival hyperplasia include

- acute myeloid leukaemia (myelomonocytic and monocytic types)

# NYSTAGMUS

Upbeat nystagmus

- cerebellar vermis lesions

Downbeat nystagmus - foramen magnum lesions

- Arnold-Chiari malformation

# 5-HT3 ANTAGONISTS

5-HT3 antagonists are antiemetics used mainly in the management of chemotherapy-related nausea. They mainly act in the chemoreceptor trigger zone area of the medulla oblongata.

Examples
- ondansetron
- granisetron

Adverse effects
- constipation is common
- prolonged QT interval

# CADASIL

Overview
- Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)
- rare cause of multi-infarct dementia
- patients often present with migraine

# CEREBROSPINAL FLUID: RAISED LYMPHOCYTES

Normal values of cerebrospinal fluid (CSF) are as follows:
- pressure = 60-150 mm (patient recumbent)
- protein = 0.2-0.4 g/l
- glucose = > 2/3 blood glucose
- cells: red cells = 0, white cells < 5/mm³

The following conditions are associated with raised lymphocytes
- viral meningitis/encephalitis
- TB meningitis
- partially treated bacterial meningitis
- Lyme disease
- Behcet's, SLE
- lymphoma, leukaemia

# CEREBROSPINAL FLUID: RAISED PROTEIN

Normal values of cerebrospinal fluid (CSF) are as follows:
- pressure = 60-150 mm (patient recumbent)
- protein = 0.2-0.4 g/l
- glucose = > 2/3 blood glucose
- cells: red cells = 0, white cells < 5/mm³

The following conditions are associated with raised protein levels
- Guillain-Barre syndrome
- tuberculous, fungal and bacterial meningitis
- Froin's syndrome*
- viral encephalitis

*describes an increase in CSF protein below a spinal canal blockage (e.g. tumour, disc, infection)

# RINNE'S AND WEBER'S TEST

Performing both Rinne's and Weber's test allows differentiation of conductive and sensorineural deafness.

Rinne's test

- tuning fork is placed over the mastoid process until the sound is no longer heard, followed by repositioning just over external acoustic meatus
- 'positive test': air conduction (AC) is normally better than bone conduction (BC)
- 'negative test': if BC > AC then conductive deafness

Weber's test
- tuning fork is placed in the middle of the forehead equidistant from the patient's ears
- the patient is then asked which side is loudest
- in unilateral sensorineural deafness, sound is localised to the unaffected side
- in unilateral conductive deafness, sound is localised to the affected side

# NERVE CONDUCTION STUDIES

Nerve conduction studies (NCS) are useful in determining between axonal and demyelinating pathology

Axonal
- normal conduction velocity
- reduced amplitude

Demyelinating
- reduced conduction velocity
- normal amplitude

# DVLA: NEUROLOGICAL DISORDERS

The guidelines below relate to car/motorcycle use unless specifically stated. For obvious reasons, the rules relating to drivers of heavy goods vehicles tend to be much stricter

Epilepsy/seizures - all patient must not drive and must inform the DVLA
- first unprovoked/isolated seizure: 6 months off if there are no relevant structural abnormalities on brain imaging and no definite epileptiform activity on EEG. If these conditions are not met then this is increased to 12 months
- for patients with established epilepsy or those with multiple unprovoked seizures:
- → may qualify for a driving licence if they have been free from any seizure for 12 months
- → if there have been no seizures for 5 years (with medication if necessary) a ’til 70 licence is usually restored
- withdrawawl of epilepsy medication: should not drive whilst anti-epilepsy medication is being withdrawn and for 6 months after the last dose

Syncope
- simple faint: no restriction
- single episode, explained and treated: 4 weeks off
- single episode, unexplained: 6 months off
- two or more episodes: 12 months off

Other conditions
- stroke or TIA: 1 month off driving, may not need to inform DVLA if no residual neurological deficit
- multiple TIAs over short period of times: 3 months off driving and inform DVLA
- craniotomy e.g. For meningioma: 1 year off driving*
- pituitary tumour: craniotomy: 6 months; trans-sphenoidal surgery 'can drive when there is no debarring residual impairment likely to affect safe driving'
- narcolepsy/cataplexy: cease driving on diagnosis, can restart once 'satisfactory control of symptoms'
- chronic neurological disorders e.g. multiple sclerosis, motor neuron disease: DVLA should be informed, complete PK1 form (application for driving licence holders state of health)

*if the tumour is a benign meningioma and there is no seizure history, licence can be reconsidered 6 months after surgery if remains seizure free

# PASSMEDICINE NOTES OPHTHALMOLOGY

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# SUDDEN LOSS OF VISION

Sudden loss is a frightening symptom for patients. It may represent an ongoing issue or only be temporary. The term transient monocular visual loss (TVML) describes a sudden, transient loss of vision that lasts less than 24 hours.

The most common causes of a sudden painless loss of vision are as follows:

- ischaemic/vascular (e.g. thrombosis, embolism, temporal arteritis etc). This includes recognised syndromes e.g. occlusion of central retinal vein and occlusion of central retinal artery
- vitreous haemorrhage
- retinal detachment
- retinal migraine

Ischaemic/vascular

- often referred to as 'amaurosis fugax'
- wide differential including large artery disease (atherothrombosis, embolus, dissection), small artery occlusive disease (anterior ischemic optic neuropathy, vasculitis e.g. temporal arteritis), venous disease and hypoperfusion
- may represent a form of transient ischaemic attack (TIA). It should therefore be treated in a similar fashion, with aspirin 300mg being given
- altitudinal field defects are often seen: 'curtain coming down'
- ischaemic optic neuropathy is due to occlusion of the short posterior ciliary arteries, causing damage to the optic nerve

Central retinal vein occlusion

- incidence increases with age, more common than arterial occlusion
- causes: glaucoma, polycythaemia, hypertension
- severe retinal haemorrhages are usually seen on fundoscopy

Central retinal artery occlusion

- due to thromboembolism (from atherosclerosis) or arteritis (e.g. temporal arteritis)
- features include afferent pupillary defect, 'cherry red' spot on a pale retina

Vitreous haemorrhage

- causes: diabetes, bleeding disorders, anticoagulants
- features may include sudden visual loss, dark spots

Retinal detachment

- features of vitreous detachment, which may precede retinal detachment, include flashes of light or floaters (see below)

**Differentiating posterior vitreous detachment, retinal detachment and vitreous haemorrhage**

| Posterior vitreous detachment | Retinal detachment | Vitreous haemorrhage |
|---|---|---|
| Flashes of light (photopsia) - in the peripheral field of vision<br>Floaters, often on the temporal side of the central vision | Dense shadow that starts peripherally progresses towards the central vision<br>A veil or curtain over the field of vision<br>Straight lines appear curved<br>Central visual loss | Large bleeds cause sudden visual loss<br>Moderate bleeds may be described as numerous dark spots<br>Small bleeds may cause floaters |

# TUNNEL VISION

Tunnel vision is the concentric diminution of the visual fields

Causes
- papilloedema
- glaucoma
- retinitis pigmentosa
- choroidoretinitis
- optic atrophy secondary to tabes dorsalis
- hysteria

# ORBITAL CELLULITIS

Orbital cellulitis is the result of an infection affecting the fat and muscles posterior to the orbital septum, within the orbit but not involving the globe. It is usually caused by a spreading upper respiratory tract infection from the sinuses and carries a high mortality rate. Orbital cellulitis is a medical emergency requiring hospital admission and urgent senior review. Periorbital (preseptal) cellulitis is a less serious superficial infection anterior to the orbital septum, resulting from a superficial tissue injury (chalazion, insect bite etc...). Periorbital cellulitis can progress to orbital cellulitis.

Epidemiology
- Mean age of hospitalisation 7-12 years.

Risk factors
- Childhood
- Previous sinus infection
- Lack of Haemophilus influenzae type b (Hib) vaccination
- Recent eyelid infection/ insect bite on eyelid (Peri-orbital cellulitis)
- Ear or facial infection

Presentation
- Redness and swelling around the eye
- Severe ocular pain
- Visual disturbance
- Proptosis
- Ophthalmoplegia/pain with eye movements
- Eyelid oedema and ptosis
- Drowsiness +/- Nausea/vomiting in meningeal involvement (Rare)

Differentiating orbital from preseptal cellulitis
- reduced visual acuity, proptosis, ophthalmoplegia/pain with eye movements are NOT consistent with preseptal cellulitis

Investigations
- Full blood count – WBC elevated, raised inflammatory markers.
- Clinical examination involving complete ophthalmological assessment – Decreased vision, afferent pupillary defect, proptosis, dysmotility, oedema, erythema.
- CT with contrast – Inflammation of the orbital tissues deep to the septum, sinusitis.
- Blood culture and microbiological swab to determine the organism. Most common bacterial causes – Streptococcus, Staphylococcus aureus, Haemophilus influenzae B.

Management
- admission to hospital for IV antibiotics

# RED EYE

There are many possible causes of a red eye. It is important to be able to recognise the causes which require urgent referral to an ophthalmologist. Below is a brief summary of the key distinguishing features

Acute angle closure glaucoma

- severe pain (may be ocular or headache)
- decreased visual acuity, patient sees haloes
- semi-dilated pupil
- hazy cornea

Anterior uveitis

- acute onset
- pain
- blurred vision and photophobia
- small, fixed oval pupil, ciliary flush

Scleritis

- severe pain (may be worse on movement) and tenderness
- may be underlying autoimmune disease e.g. rheumatoid arthritis

Conjunctivitis

- purulent discharge if bacterial, clear discharge if viral

Subconjunctival haemorrhage

- history of trauma or coughing bouts

Endophthalmitis

- typically red eye, pain and visual loss following intraocular surgery

# ACUTE ANGLE CLOSURE GLAUCOMA

Glaucoma is a group of disorders characterised by optic neuropathy due, in the majority of patients, to raised intraocular pressure (IOP). It is now recognised that a minority of patients with raised IOP do not have glaucoma and vice versa.

In acute angle-closure glaucoma (AACG) there is a rise in IOP secondary to an impairment of aqueous outflow. Factors predisposing to AACG include:
- hypermetropia (long-sightedness)
- pupillary dilatation
- lens growth associated with age

Features
- severe pain: may be ocular or headache
- decreased visual acuity
- symptoms worse with mydriasis (e.g. watching TV in a dark room)
- hard, red-eye
- haloes around lights
- semi-dilated non-reacting pupil
- corneal oedema results in dull or hazy cornea
- systemic upset may be seen, such as nausea and vomiting and even abdominal pain

Management
- urgent referral to an ophthalmologist
- management options include reducing aqueous secretions with acetazolamide and inducing pupillary constriction with topical pilocarpine

# PRIMARY OPEN-ANGLE GLAUCOMA

Glaucomas are optic neuropathies associated with raised intraocular pressure (IOP). They can be classified based on whether the peripheral iris is covering the trabecular meshwork, which is important in the drainage of aqueous humour from the anterior chamber of the eye. In open-angle glaucoma, the iris is clear of the meshwork. The trabecular network functionally offers an increased resistance to aqueous outflow, causing increased IOP. It is now recognised that a minority of patients with raised IOP do not have glaucoma and vice versa.

Epidemiology
- affects 0.5% of people over the age of 40
- the prevalence increases with age up to 10% over the age of 80 years
- affects males and females equally

Primary open-angle glaucoma (POAG, also referred to as chronic simple glaucoma) is present in around 2% of people older than 40 years. Other than age, risk factors include:

- genetics: first degree relatives of an open-angle glaucoma patient have a 16% chance of developing the disease
- black patients
- myopia
- hypertension
- diabetes mellitus
- corticosteroids

POAG may present insidiously and for this reason is often detected during routine optometry appointments. Features may include

- peripheral visual field loss - nasal scotomas progressing to 'tunnel vision'
- decreased visual acuity
- optic disc cupping

Fundoscopy signs of primary open-angle glaucoma (POAG):
1. Optic disc cupping - cup-to-disc ratio >0.7 (normal = 0.4-0.7), occurs as loss of disc substance makes optic cup widen and deepen
2. Optic disc pallor - indicating optic atrophy
3. Bayonetting of vessels - vessels have breaks as they disappear into the deep cup and re-appear at the base
4. Additional features - Cup notching (usually inferior where vessels enter disc), Disc haemorrhages

Diagnosis:

- Case finding and provisional diagnosis is done by an optometrist
- Referral to the ophthalmologist is done via the GP
- Final diagnosis is done by investigations as below

Investigations:

- automated perimetry to assess visual field
- slit lamp examination with pupil dilatation to assess optic neve and fundus for a baseline
- applanation tonometry to measure IOP
- central corneal thickness measurement
- gonioscopy to assess peripheral anterior chamber configuration and depth
- Assess risk of future visual impairment, *using risk factors such as IOP, central corneal thickness (CCT), family history, life expectancy*

## PRIMARY OPEN-ANGLE GLAUCOMA: MANAGEMENT

Glaucomas are optic neuropathies associated with raised intraocular pressure (IOP). They can be classified based on whether the peripheral iris is covering the trabecular meshwork, which is important in the drainage of aqueous humour from the anterior chamber of the eye. In open-angle glaucoma, the iris is clear of the meshwork. The trabecular network functionally offers an increased resistance to aqueous outflow, causing increased IOP.

Epidemiology
- affects 0.5% of people over the age of 40
- the prevalence increases with age up to 10% over the age of 80 years
- affects males and females equally

Causes
- increasing age
- genetics: first degree relatives of an open-angle glaucoma patient have a 16% chance of developing the disease

Symptoms:
- characterised by a slow rise in intraocular pressure: symptomless for a long period
- typically present following an ocular pressure measurement during a routine examination by an optometrist

Signs:
- increased intraocular pressure
- visual field defect
- pathological cupping of the optic disc1

Case finding:
- optic nerve head damage visible under the slit lamp
- visual field defect
- IOP > 24 mmHg as measured by Goldmann-type applanation tonometry
- if suspected full investigations are performed

Diagnosis:
- Case finding and provisional diagnosis is done by an optometrist
- Referral to the ophthalmologist is done via the GP
- Final diagnosis is done by investigations as below

Investigations:
- automated perimetry to assess visual field
- slit lamp examination with pupil dilatation to assess optic neve and fundus for a baseline
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- gonioscopy to assess peripheral anterior chamber configuration and depth
- Assess risk of future visual impairment, using risk factors such as IOP, central corneal thickness (CCT), family history, life expectancy

The majority of patients with primary open-angle glaucoma are managed with eye drops. These aim to lower intra-ocular pressure which in turn has been shown to prevent progressive loss of visual field.

NICE guidelines:

- first line: prostaglandin analogue (PGA) eyedrop
- second line: beta-blocker, carbonic anhydrase inhibitor, or sympathomimetic eyedrop
- if more advanced: surgery or laser treatment can be tried2

Reassessment

- important to exclude progression and visual field loss
- needs to be done more frequently if: IOP uncontrolled, the patient is high risk, or there is progression
-

| Medication | Mode of action | Notes |
|---|---|---|
| Prostaglandin analogues (e.g. latanoprost) | Increases uveoscleral outflow | Once daily administration<br>Adverse effects include brown pigmentation of the iris, increased eyelash length |
| Beta-blockers (e.g. timolol, betaxolol) | Reduces aqueous production | Should be avoided in asthmatics and patients with heart block |
| Sympathomimetics (e.g. brimonidine, an alpha2-adrenoceptor agonist) | Reduces aqueous production and increases outflow | Avoid if taking MAOI or tricyclic antidepressants<br>Adverse effects include hyperaemia |
| Carbonic anhydrase inhibitors (e.g. Dorzolamide) | Reduces aqueous production | Systemic absorption may cause sulphonamide-like reactions |
| Miotics (e.g. pilocarpine, a muscarinic receptor agonist) | Increases uveoscleral outflow | Adverse effects included a constricted pupil, headache and blurred vision |

Surgery in the form of a trabeculectomy may be considered in refractory cases.

# ANTERIOR UVEITIS

Anterior uveitis is one of the important differentials of a red eye. It is also referred to as iritis. Anterior uveitis describes inflammation of the anterior portion of the uvea - iris and ciliary body. It is associated with HLA-B27 and may be seen in association with other HLA-B27 linked conditions (see below).

Features
- acute onset
- ocular discomfort & pain (may increase with use)
- pupil may be irregular and small
- photophobia (often intense)
- blurred vision
- red eye
- lacrimation
- ciliary flush
- hypopyon; describes pus and inflammatory cells in the anterior chamber, often resulting in a visible fluid level
- visual acuity initially normal → impaired

Associated conditions
- ankylosing spondylitis
- reactive arthritis
- ulcerative colitis, Crohn's disease
- Behcet's disease
- sarcoidosis: bilateral disease may be seen

Management
- urgent review by ophthalmology
- cycloplegics (dilates the pupil which helps to relieve pain and photophobia) e.g. Atropine, cyclopentolate
- steroid eye drops

# BLEPHARITIS

Blepharitis is inflammation of the eyelid margins. It may due to either meibomian gland dysfunction (common, posterior blepharitis) or seborrhoeic dermatitis/staphylococcal infection (less common, anterior blepharitis). Blepharitis is also more common in patients with rosacea

The meibomian glands secrete oil on to the eye surface to prevent rapid evaporation of the tear film. Any problem affecting the meibomian glands (as in blepharitis) can hence cause drying of the eyes which in turns leads to irritation

Features

- symptoms are usually bilateral
- grittiness and discomfort, particularly around the eyelid margins
- eyes may be sticky in the morning
- eyelid margins may be red. Swollen eyelids may be seen in staphylococcal blepharitis
- styes and chalazions are more common in patients with blepharitis
- secondary conjunctivitis may occur

Management

- softening of the lid margin using hot compresses twice a day
- 'lid hygiene' - mechanical removal of the debris from lid margins
  - cotton wool buds dipped in a mixture of cooled boiled water and baby shampoo is often used
  - an alternative is sodium bicarbonate, a teaspoonful in a cup of cooled water that has recently been boiled
- artificial tears may be given for symptom relief in people with dry eyes or an abnormal tear film

# LACRIMAL DUCT PROBLEMS

**Dacryocystitis** is infection of the lacrimal sac

Features
- watering eye (epiphora)
- swelling and erythema at the inner canthus of the eye

Management is with systemic antibiotics. Intravenous antibiotics are indicated if there is associated periorbital cellulitis

**Congenital lacrimal duct obstruction** affects around 5-10% of newborns. It is bilateral in around 20% of cases

Features
- watering eye (even if not crying)
- secondary infection may occur

Symptoms resolve in 99% of cases by 12 months of age

# CATARACTS

A cataract is a common eye condition where the lens of the eye gradually opacifies i.e. becomes cloudy. This cloudiness makes it more difficult for light to reach the back of the eye (retina), thus causing reduced/blurred vision. Cataracts are the leading cause of curable blindness worldwide.

Epidemiology
- Cataracts are more common in women than in men
- The incidence of cataracts increases with age. One study found that 30% of individuals aged 65 and over had a visually-impairing cataract in either one or both eyes

Causes
- Normal ageing process: most common cause

Other possible causes
- Smoking
- Increased alcohol consumption
- Trauma
- Diabetes mellitus
- Long-term corticosteroids
- Radiation exposure
- Myotonic dystrophy
- Metabolic disorders: hypocalcaemia

Patients typically present with a gradual onset of:
- Reduced vision
- Faded colour vision: making it more difficult to distinguish different colours
- Glare: lights appear brighter than usual
- Halos around lights

Signs:
- A Defect in the red reflex: the red reflex is essentially the reddish-orange reflection seen through an ophthalmoscope when a light is shone on the retina. Cataracts will prevent light from getting to the retina, hence you see a defect in the red reflex.

Investigations:
- Ophthalmoscopy: done after pupil dilation. Findings: normal fundus and optic nerve
- Slit-lamp examination. Findings: visible cataract

Classification
- Nuclear: change lens refractive index, common in old age
- Polar: localized, commonly inherited, lie in the visual axis
- Subcapsular: due to steroid use, just deep to the lens capsule, in the visual axis

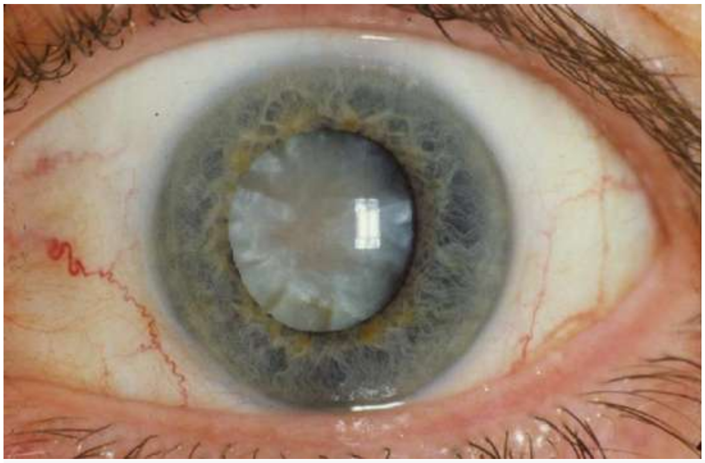
- Dot opacities: common in normal lenses, also seen in diabetes and myotonic dystrophy

Management

- Non-surgical: In the early stages, age-related cataracts can be managed conservatively by prescribing stronger glasses/contact lens, or by encouraging the use of brighter lighting. These options help optimise vision but do not actually slow down the progression of cataracts, therefore surgery will eventually be needed.
- Surgery: Surgery is the only effective treatment for cataracts. This involves removing the cloudy lens and replacing this with an artificial one. NICE suggests that referral for surgery should be dependent upon whether a visual impairment is present, impact on quality of life, and patient choice. Also whether both eyes are affected and the possible risks and benefits of surgery should be taken into account. Prior to cataract surgery, patients should be provided with information on the refractive implications of various types of intraocular lenses. After cataract surgery, patients should be advised on the use of eye drops and eyewear, what to do if vision changes and the management of other ocular problems. Cataract surgery has a high success rate with 85-90% of patients achieving 6/12 corrected vision (on a Snellen chart) postoperatively.

Complications following surgery

- Posterior capsule opacification: thickening of the lens capsule
- Retinal detachment
- Posterior capsule rupture
- Endophthalmitis: inflammation of aqueous and/or vitreous humour



A hypermature age-related cortico-nuclear cataract with a brunescent (brown) nucleus. Credit National Eye Institute, National Institutes of Health.

# KERATITIS

Keratitis describes inflammation of the cornea. Microbial keratitis is not like conjunctivitis - it is potentially sight threatening and should therefore be urgently evaluated and treated.

## Aetiology

Causes
- bacterial
  - typically Staphylococcus aureus
  - Pseudomonas aeruginosa is seen in contact lens wearers
- fungal
- amoebic
  - acanthamoebic keratitis
  - accounts for around 5% of cases
  - increased incidence if eye exposure to soil or contaminated water
- parasitic: onchocercal keratitis ('river blindness')

Remember, other factors may causes keratitis:
  - viral: herpes simplex keratitis
  - environmental
- photokeratitis: e.g. welder's arc eye
- exposure keratitis
- contact lens acute red eye (CLARE)

## Clinical features

Features
- red eye: pain and erythema
- photophobia
- foreign body, gritty sensation
- hypopyon may be seen

## Evaluation and management

Referral
- contact lens wearers
  - assessing contact lens wearers who present with a painful red eye is difficult
  - an accurate diagnosis can only usually be made with a slit-lamp, meaning same-day referral to an eye specialist is usually required to rule out microbial keratitis

Management
- stop using contact lens until the symptoms have fully resolved

- topical antibiotics
    - typically quinolones are used first-line
- cycloplegic for pain relief
    - e.g. cyclopentolate

Complications may include:
- corneal scarring
- perforation
- endophthalmitis
- visual loss

# MYDRIASIS

Causes of mydriasis (large pupil)
- third nerve palsy
- Holmes-Adie pupil
- traumatic iridoplegia
- phaeochromocytoma
- congenital

Drug causes of mydriasis
- topical mydriatics: tropicamide, atropine
- sympathomimetic drugs: amphetamines, cocaine
- anticholinergic drugs: tricyclic antidepressants

Anisocoria may result in apparent mydriasis, due to the difference with the other pupil.

# RELATIVE AFFERENT PUPILLARY DEFECT

Also known as the Marcus-Gunn pupil, a relative afferent pupillary defect is found by the 'swinging light test'. It is caused by a lesion anterior to the optic chiasm i.e. optic nerve or retina

Finding
- the affected and normal eye appears to dilate when light is shone on the affected

Causes
- retina: detachment
- optic nerve: optic neuritis e.g. multiple sclerosis

Pathway of pupillary light reflex
- afferent: retina → optic nerve → lateral geniculate body → midbrain
- efferent: Edinger-Westphal nucleus (midbrain) → oculomotor nerve

# ARGYLL-ROBERTSON PUPIL

Argyll-Robertson pupil is one of the classic pupillary syndrome. It is sometimes seen in neurosyphilis. A mnemonic used for the Argyll-Robertson Pupil (ARP) is Accommodation Reflex Present (ARP) but Pupillary Reflex Absent (PRA)

Features

- small, irregular pupils
- no response to light but there is a response to accommodate

Causes

- diabetes mellitus
- syphilis

# HOLMES-ADIE PUPIL

Holmes-Adie pupil is a benign condition most commonly seen in women. It is one of the differentials of a dilated pupil.

Overview

- unilateral in 80% of cases
- dilated pupil
- once the pupil has constricted it remains small for an abnormally long time
- slowly reactive to accommodation but very poorly (if at all) to light

Holmes-Adie syndrome

- association of Holmes-Adie pupil with absent ankle/knee reflexes

# HORNER'S SYNDROME

Features

- miosis (small pupil)
- ptosis
- enophthalmos* (sunken eye)
- anhidrosis (loss of sweating one side)

Distinguishing between causes

- heterochromia (difference in iris colour) is seen in congenital Horner's
- anhidrosis: see below

| Central lesions | Pre-ganglionic lesions | Post-ganglionic lesions |
|---|---|---|
| Anhidrosis of the face, arm and trunk | Anhidrosis of the face | No anhidrosis |
| **S**troke<br>**S**yringomyelia<br>Multiple **s**clerosis<br>Tumour<br>Encephalitis | Pancoast's **t**umour<br>**T**hyroidectomy<br>**T**rauma<br>Cervical rib | **C**arotid artery dissection<br>**C**arotid aneurysm<br>**C**avernous sinus thrombosis<br>**C**luster headache |

*in reality the appearance is due to a narrow palpebral aperture rather than true enophthalmos

# AGE RELATED MACULAR DEGENERATION

Age-related macular degeneration is the most common cause of blindness in the UK. Degeneration of the central retina (macula) is the key feature with changes usually bilateral. ARMD is characterised by degeneration of retinal photoreceptors that results in the formation of drusen which can be seen on fundoscopy and retinal photography.

Traditionally two forms of macular degeneration are seen:
- dry (90% of cases, geographic atrophy) macular degeneration: characterised by drusen - yellow round spots in Bruch's membrane
- wet (10% of cases, exudative, neovascular) macular degeneration: characterised by choroidal neovascularisation. Leakage of serous fluid and blood can subsequently result in a rapid loss of vision. Carries worst prognosis

Recently there has been a move to a more updated classification:
- early age-related macular degeneration (non-exudative, age-related maculopathy): drusen and alterations to the retinal pigment epithelium (RPE)
- late age-related macular degeneration (neovascularisation, exudative)

Age-related macular degeneration (ARMD) is the commonest cause of visual loss in elderly persons in the developed world. It affects 30-50 million people worldwide.

Epidemiology
- population estimates suggest a male to female ratio of 1:2
- the average age of presentation is greater than 70 years of age

Risk factors
- Advancing age itself is the greatest risk factor for ARMD. The risk of ARMD increases 3 fold for patients aged older than 75 years, versus those aged 65-74.
- Smoking is another key risk factor in the development of ARMD, current smokers are twice as likely as non-smokers to have ARMD related visual loss, and ex-smokers have a slightly increased risk of developing the condition, (OR 1.13).
- Family history is also a strong risk factor for developing ARMD. First degree relatives of a sufferer of ARMD are thought to be four times more likely to inherit the condition.
- Other risk factors for developing the condition include those associated with increased risk of ischaemic cardiovascular disease, such as hypertension, dyslipidaemia and diabetes mellitus.

Patients typically present with a subacute onset of visual loss with:
- a reduction in visual acuity, particularly for near field objects
- difficulties in dark adaptation with an overall deterioration in vision at night
- fluctuations in visual disturbance which may vary significantly from day to day
- they may also suffer from photopsia, (a perception of flickering or flashing lights), and glare around objects

Signs:

- distortion of line perception may be noted on Amsler grid testing
- fundoscopy reveals the presence of drusen, yellow areas of pigment deposition in the macular area, which may become confluent in late disease to form a macular scar.
- in wet ARMD well demarcated red patches may be seen which represent intra-retinal or sub-retinal fluid leakage or haemorrhage.

Investigations:

- slit-lamp microscopy is the initial investigation of choice, to identify any pigmentary, exudative or haemorrhagic changes affecting the retina which may identify the presence of ARMD. This is usually accompanied by colour fundus photography to provide a baseline against which changes can be identified over time.
- fluorescein angiography is utilised if neovascular ARMD is suspected, as this can guide intervention with anti-VEGF therapy. This may be complemented with indocyanine green angiography to visualise any changes in the choroidal circulation.
- ocular coherence tomography is used to visualise the retina in three dimensions, because it can reveal areas of disease which aren't visible using microscopy alone.

Treatment:

- the AREDS trial examined the treatment of dry ARMD in 3640 subjects. It showed that a combination of zinc with anti-oxidant vitamins A,C and E reduced progression of the disease by around one third. Patients with more extensive drusen seemed to benefit most from the intervention. Treatment is therefore recommended in patients with at least moderate category dry ARMD.
- Vascular endothelial growth factor, (VEGF) is a potent mitogen and drives increased vascular permeability in patients with wet ARMD. A number of trials have shown that use of anti-VEGF agents can limit progression of wet ARMD and stabilise or reverse visual loss. Evidence suggests that they should be instituted within the first two months of diagnosis of wet ARMD if possible. Examples of anti-VEGF agents include ranibizumab, bevacizumab and pegaptanib,. The agents are usually administered by 4 weekly injection.
- Laser photocoagulation does slow progression of ARMD where there is new vessel formation, although there is a risk of acute visual loss after treatment, which may be increased in patients with sub-foveal ARMD. For this reason anti-VEGF therapies are usually preferred.

# PAPILLOEDEMA

Papilloedema describes optic disc swelling that is caused by increased intracranial pressure. It is almost always bilateral.

The following features may be observed during fundoscopy:
- venous engorgement: usually the first sign
- loss of venous pulsation: although many normal patients do not have normal pulsation
- blurring of the optic disc margin
- elevation of optic disc
- loss of the optic cup
- Paton's lines: concentric/radial retinal lines cascading from the optic disc

Causes of papilloedema
- space-occupying lesion: neoplastic, vascular
- malignant hypertension
- idiopathic intracranial hypertension
- hydrocephalus
- hypercapnia

Rare causes include
- hypoparathyroidism and hypocalcaemia
- vitamin A toxicity

# HYPERTENSIVE RETINOPATHY

The table below shows the Keith-Wagener classification of hypertensive retinopathy

| Stage | Features |
|---|---|
| I | Arteriolar narrowing and tortuosity<br>Increased light reflex - silver wiring |
| II | Arteriovenous nipping |
| III | Cotton-wool exudates<br>Flame and blot haemorrhages |
| IV | Papilloedema |

# DIABETIC RETINOPATHY

Diabetic retinopathy is the most common cause of blindness in adults aged 35-65 years-old. Hyperglycaemia is thought to cause increased retinal blood flow and abnormal metabolism in the retinal vessel walls. This precipitates damage to endothelial cells and pericytes

Endothelial dysfunction leads to increased vascular permeability which causes the characteristic exudates seen on fundoscopy. Pericyte dysfunction predisposes to the formation of microaneurysms. Neovasculization is thought to be caused by the production of growth factors in response to retinal ischaemia

In exams you are most likely to be asked about the characteristic features of the various stages/types of diabetic retinopathy. Recently a new classification system has been proposed, dividing patients into those with non-proliferative diabetic retinopathy (NPDR) and those with proliferative retinopathy (PDR):

| Traditional classification | New classification |
|---|---|
| Background retinopathy<br>• microaneurysms (dots)<br>• blot haemorrhages (<=3)<br>• hard exudates<br>Pre-proliferative retinopathy<br>• cotton wool spots (soft exudates; ischaemic nerve fibres)<br>• > 3 blot haemorrhages<br>• venous beading/looping<br>• deep/dark cluster haemorrhages<br>• more common in Type I DM, treat with laser photocoagulation | Mild NPDR<br>• 1 or more microaneurysm<br>Moderate NPDR<br>• microaneurysms<br>• blot haemorrhages<br>• hard exudates<br>• cotton wool spots, venous beading/looping and intraretinal microvascular abnormalities (IRMA) less severe than in severe NPDR<br>Severe NPDR<br>• blot haemorrhages and microaneurysms in 4 quadrants<br>• venous beading in at least 2 quadrants<br>• IRMA in at least 1 quadrant |

Proliferative retinopathy

- retinal neovascularisation - may lead to vitrous haemorrhage
- fibrous tissue forming anterior to retinal disc

- more common in Type I DM, 50% blind in 5 years

Maculopathy

- based on location rather than severity, anything is potentially serious
- hard exudates and other 'background' changes on macula
- check visual acuity
- more common in Type II DM

# POSTERIOR VITREOUS DETACHMENT

Posterior vitreous detachment is the separation of the vitreous membrane from the retina. This occurs due to natural changes to the vitreous fluid of the eye with ageing. Posterior vitreous detachment is a common condition that does not cause any pain or loss of vision. However, rarely the separation of the vitreous membrane can lead to tears and detachment of the retina. It is important to rule out retinal tears or retinal detachment in anyone with suspected posterior vitreous detachment, as they may result in permanent loss of vision.

Epidemiology:
- Occur in over 75% of people over the age of 65
- More common in females

Risk factors:
- As people age, the vitreous fluid in the eye becomes less viscous, and thus, does not hold its shape as well. Therefore, it pulls the vitreous membrane away from the retina towards the centre of the eye.
- Highly myopic (near-sighted) patients are also at increased risk of developing posterior vitreous detachment earlier in life. This is because the myopic eye has a longer axial length than an emmetropic eye.

Symptoms:
- The sudden appearance of floaters (occasionally a ring of floaters temporal to central vision)
- Flashes of light in vision
- Blurred vision
- Cobweb across vision
- The appearance of a dark curtain descending down vision (means that there is also retinal detachment)

Signs:
- Weiss ring on ophthalmoscopy (the detachment of the vitreous membrane around the optic nerve to form a ring-shaped floater).

Investigations:
- All patients with suspected vitreous detachment should be examined by an ophthalmologist within 24hours to rule out retinal tears or detachment.

Management:
- Posterior vitreous detachment alone does not cause any permanent loss of vision. Symptoms gradually improve over a period of around 6 months and therefore no treatment is necessary.
- If there is an associated retinal tear or detachment the patient will require surgery to fix this.

# OPTIC ATROPHY

Optic atrophy is seen as pale, well demarcated disc on fundoscopy. It is usually bilateral and causes a gradual loss of vision*. Causes may be acquired or congenital

Acquired causes

- multiple sclerosis
- papilloedema (longstanding)
- raised intraocular pressure (e.g. glaucoma, tumour)
- retinal damage (e.g. choroiditis, retinitis pigmentosa)
- ischaemia
- toxins: tobacco amblyopia, quinine, methanol, arsenic, lead
- nutritional: vitamin B1, B2, B6 and B12 deficiency

Congenital causes

- Friedreich's ataxia
- mitochondrial disorders e.g. Leber's optic atrophy
- DIDMOAD - the association of cranial Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness (also known as Wolfram's syndrome)

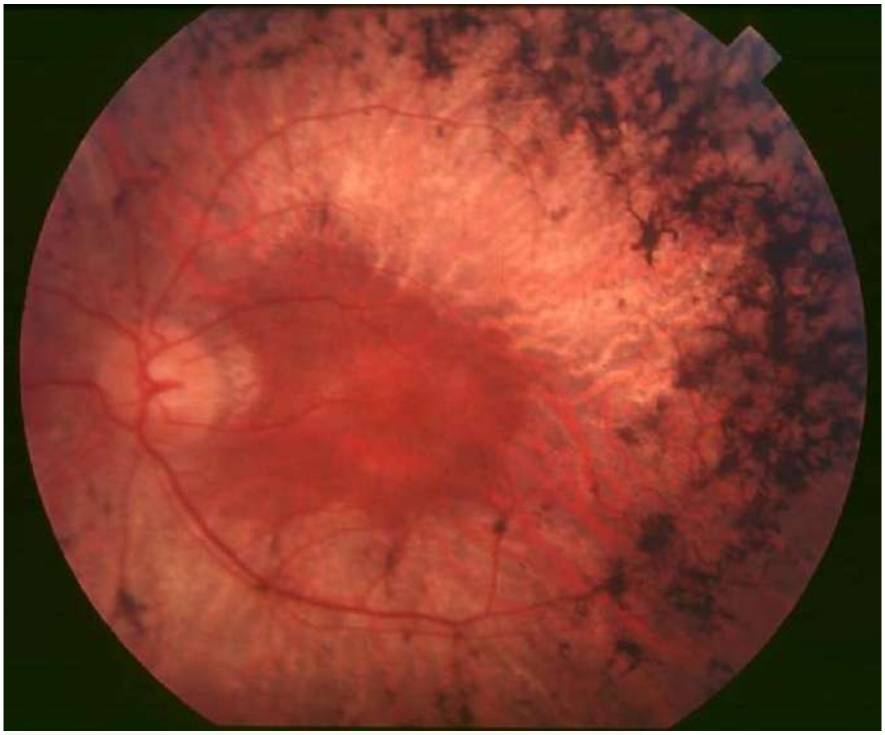
*strictly speaking optic atrophy is a descriptive term, it is the optic neuropathy that results in visual loss

# RETINITIS PIGMENTOSA

Retinitis pigmentosa primarily affects the peripheral retina resulting in tunnel vision

Features
- night blindness is often the initial sign
- tunnel vision due to loss of the peripheral retina (occasionally referred to as funnel vision)
- fundoscopy: black bone spicule-shaped pigmentation in the peripheral retina, mottling of the retinal pigment epithelium

Associated diseases
- Refsum disease: cerebellar ataxia, peripheral neuropathy, deafness, ichthyosis
- Usher syndrome
- abetalipoproteinemia
- Lawrence-Moon-Biedl syndrome
- Kearns-Sayre syndrome
- Alport's syndrome



Fundus showing changes secondary to retinitis pigmentosa

# CENTRAL RETINAL ARTERY OCCLUSION

Central retinal artery occlusion

- causes sudden unilateral visual loss
- due to thromboembolism (from atherosclerosis) or arteritis (e.g. temporal arteritis)
- features include afferent pupillary defect, 'cherry red' spot on a pale retina

# CENTRAL RETINAL VEIN OCCLUSION

Central retinal vein occlusion (CRVO) is a differential for sudden painless loss of vision.

Risk factors

- increasing age
- glaucoma
- polycythaemia

Features

- sudden, painless reduction or loss of visual acuity, usually unilaterally
- severe retinal haemorrhages are usually seen on fundoscopy

# ANGIOID RETINAL STREAKS

Angioid retinal streaks are seen on fundoscopy as irregular dark red streaks radiating from the optic nerve head. They are caused by degeneration, calcification and breaks in Bruch's membrane .

Causes

- pseudoxanthoma elasticum
- Ehler-Danlos syndrome
- Paget's disease
- sickle-cell anaemia
- acromegaly

# OPTIC NEURITIS

Causes

- multiple sclerosis
- diabetes
- syphilis

Features

- unilateral decrease in visual acuity over hours or days
- poor discrimination of colours, 'red desaturation'
- pain worse on eye movement
- relative afferent pupillary defect
- central scotoma

Management

- high-dose steroids
- recovery usually takes 4-6 weeks

Prognosis

- MRI: if > 3 white-matter lesions, 5-year risk of developing multiple sclerosis is c. 50%

# HERPES ZOSTER OPHTHALMICUS

Herpes zoster ophthalmicus (HZO) describes the reactivation of the varicella-zoster virus in the area supplied by the ophthalmic division of the trigeminal nerve. It accounts for around 10% of case of shingles.

Features
- vesicular rash around the eye, which may or may not involve the actual eye itself
- Hutchinson's sign: rash on the tip or side of the nose. Indicates nasociliary involvement and is a strong risk factor for ocular involvement

Management
- oral antiviral treatment for 7-10 days
    - ideally started within 72 hours
    - intravenous antivirals may be given for very severe infection or if the patient is immunocompromised
    - topical antiviral treatment is not given in HZO
- topical corticosteroids may be used to treat any secondary inflammation of the eye
- ocular involvement requires urgent ophthalmology review

Complications
- ocular: conjunctivitis, keratitis, episcleritis, anterior uveitis
- ptosis
- post-herpetic neuralgia

# HERPES SIMPLEX KERATITIS

Herpes simplex keratitis most commonly presents with a dendritic corneal ulcer.

Features
- red, painful eye
- photophobia
- epiphora
- visual acuity may be decreased
- fluorescein staining may show an epithelial ulcer

Management
- immediate referral to an ophthalmologist
- topical aciclovir

# RHEUMATOID ARTHRITIS: OCULAR MANIFESTATIONS

Ocular manifestations of rheumatoid arthritis are common, with 25% of patients having eye problems

Ocular manifestations
- keratoconjunctivitis sicca (most common)
- episcleritis (erythema)
- scleritis (erythema and pain)
- corneal ulceration
- keratitis

Iatrogenic
- steroid-induced cataracts
- chloroquine retinopathy

# PASSMEDICINE NOTES PSYCHIATRY

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# DEPRESSION: SCREENING AND ASSESSMENT

**Screening**

The following two questions can be used to screen for depression

- 'During the last month, have you often been bothered by feeling down, depressed or hopeless?'
- 'During the last month, have you often been bothered by having little interest or pleasure in doing things?'

A 'yes' answer to either of the above should prompt a more in depth assessment.

**Assessment**

There are many tools to assess the degree of depression including the Hospital Anxiety and Depression (HAD) scale and the Patient Health Questionnaire (PHQ-9).

Hospital Anxiety and Depression (HAD) scale

- consists of 14 questions, 7 for anxiety and 7 for depression
- each item is scored from 0-3
- produces a score out of 21 for both anxiety and depression
- severity: 0-7 normal, 8-10 borderline, 11+ case
- patients should be encouraged to answer the questions quickly

Patient Health Questionnaire (PHQ-9)

- asks patients 'over the last 2 weeks, how often have you been bothered by any of the following problems?'
- 9 items which can then be scored 0-3
- includes items asking about thoughts of self-harm
- depression severity: 0-4 none, 5-9 mild, 10-14 moderate, 15-19 moderately severe, 20-27 severe

**NICE** use the **DSM-IV** criteria to grade depression:

- Depressed mood most of the day, nearly every day
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
- Significant weight loss or weight gain when not dieting or decrease or increase in appetite nearly every day
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- Diminished ability to think or concentrate, or indecisiveness nearly every day
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

| Subthreshold depressive symptoms | Fewer than 5 symptoms |
|---|---|
| **Mild depression** | Few, if any, symptoms in excess of the 5 required to make the diagnosis, and symptoms result in only minor functional impairment |
| **Moderate depression** | Symptoms or functional impairment are between 'mild' and 'severe' |
| **Severe depression** | Most symptoms, and the symptoms markedly interfere with functioning. Can occur with or without psychotic symptoms |

## SEASONAL AFFECTIVE DISORDER

Seasonal affective disorder (SAD) describes depression which occurs predominately around the winter months. SAD should be treated the same way as depression, therefore as per the NICE guidelines for mild depression, you would begin with psychological therapies and follow up with the patient in 2 weeks to ensure that there has been no deterioration. Following this an SSRI can be given if needed. In seasonal affective disorder, you should not give the patient sleeping tablets as this can make the symptoms worse. Finally, the evidence for light therapy is limited and as such it is not routinely recommended.

## DEPRESSION VS. DEMENTIA

Factors suggesting diagnosis of depression over dementia

- short history, rapid onset
- biological symptoms e.g. weight loss, sleep disturbance
- patient worried about poor memory
- reluctant to take tests, disappointed with results
- mini-mental test score: variable
- global memory loss (dementia characteristically causes recent memory loss)

## DEPRESSION IN OLDER PEOPLE

Older patients are less likely to complain of depressed mood

Features

- physical complaints (e.g. hypochondriasis)
- agitation
- insomnia

Management

- SSRIs are first line (adverse side-effect profile of TCAs more of an issue in the elderly)

# BENZODIAZEPINES

Benzodiazepines enhance the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) by increasing the frequency of chloride channels. They therefore are used for a variety of purposes:

- sedation
- hypnotic
- anxiolytic
- anticonvulsant
- muscle relaxant

Patients commonly develop a tolerance and dependence to benzodiazepines and care should therefore be exercised on prescribing these drugs. The Committee on Safety of Medicines advises that benzodiazepines are only prescribed for a short period of time (2-4 weeks).

The BNF gives advice on how to withdraw a benzodiazepine. The dose should be withdrawn in steps of about 1/8 (range 1/10 to 1/4) of the daily dose every fortnight. A suggested protocol for patients experiencing difficulty is given:

- switch patients to the equivalent dose of diazepam
- reduce dose of diazepam every 2-3 weeks in steps of 2 or 2.5 mg
- time needed for withdrawal can vary from 4 weeks to a year or more

If patients withdraw too quickly from benzodiazepines they may experience benzodiazepine withdrawal syndrome, a condition very similar to alcohol withdrawal syndrome. This may occur up to 3 weeks after stopping a long-acting drug. Features include:

- insomnia
- irritability
- anxiety
- tremor
- loss of appetite
- tinnitus
- perspiration
- perceptual disturbances
- seizures

$GABA_A$ drugs

- benzodiazipines increase the **frequency** of chloride channels
- barbiturates increase the **duration** of chloride channel opening

**Freq**uently **Ben**d - **Dur**ing **Barb**eque

...or...

Barbi**durat**es increase **durat**ion & **Fre**ndodiazepines increase **freq**uency

## SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND THEIR SIDE EFFECTS

Selective serotonin reuptake inhibitors (SSRIs) are considered first-line treatment for the majority of patients with depression.

- citalopram (although see below re: QT interval) and fluoxetine are currently the preferred SSRIs
- sertraline is useful post myocardial infarction as there is more evidence for its safe use in this situation than other antidepressants
- SSRIs should be used with caution in children and adolescents. Fluoxetine is the drug of choice when an antidepressant is indicated

Adverse effects

- gastrointestinal symptoms are the most common side-effect
- there is an increased risk of gastrointestinal bleeding in patients taking SSRIs. A proton pump inhibitor should be prescribed if a patient is also taking a NSAID
- patients should be counselled to be vigilant for increased anxiety and agitation after starting a SSRI
- fluoxetine and paroxetine have a higher propensity for drug interactions

Citalopram and the QT interval

- the Medicines and Healthcare products Regulatory Agency (MHRA) released a warning on the use of citalopram in 2011
- it advised that citalopram and escitalopram are associated with dose-dependent QT interval prolongation and should not be used in those with: congenital long QT syndrome; known pre-existing QT interval prolongation; or in combination with other medicines that prolong the QT interval
- the maximum daily dose is now 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment

Interactions

- NSAIDs: NICE guidelines advise 'do not normally offer SSRIs', but if given co-prescribe a proton pump inhibitor
- warfarin / heparin: NICE guidelines recommend avoiding SSRIs and considering mirtazapine
- aspirin: see above
- triptans - increased risk of serotonin syndrome
- monoamine oxidase inhibitors (MAOIs) - increased risk of serotonin syndrome

Following the initiation of antidepressant therapy patients should normally be reviewed by a doctor after 2 weeks. For patients under the age of 30 years or at increased risk of suicide they should be reviewed after 1 week. If a patient makes a good response to antidepressant therapy they should continue on treatment for at least 6 months after remission as this reduces the risk of relapse.

When stopping a SSRI the dose should be gradually reduced over a 4 week period (this is not necessary with fluoxetine). Paroxetine has a higher incidence of discontinuation symptoms.

Discontinuation symptoms
- increased mood change
- restlessness
- difficulty sleeping
- unsteadiness
- sweating
- gastrointestinal symptoms: pain, cramping, diarrhoea, vomiting
- paraesthesia

SSRIs and pregnancy
- BNF says to weigh up benefits and risk when deciding whether to use in pregnancy.
- Use during the first trimester gives a small increased risk of congenital heart defects
- Use during the third trimester can result in persistent pulmonary hypertension of the newborn
- Paroxetine has an increased risk of congenital malformations, particularly in the first trimester

## SEROTONIN AND NORADRENALINE REUPTAKE INHIBITORS

Serotonin and noradrenaline reuptake inhibitor (SNRI's) are a class of relatively new antidepressants. Inhibiting the reuptake increases the concentrations of serotonin and noradrenaline in the synaptic cleft leading to the effects. Examples include venlafaxine and duloxetine. They are used to treat major depressive disorders, generalised anxiety disorder, social anxiety disorder and panic disorder and menopausal symptoms.

## TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants (TCAs) are used less commonly now for depression due to their side-effects and toxicity in overdose. They are however used widely in the treatment of neuropathic pain, where smaller doses are typically required.

Common side-effects
- drowsiness
- dry mouth
- blurred vision
- constipation
- urinary retention
- lengthening of QT interval

Choice of tricyclic

- low-dose amitriptyline is commonly used in the management of neuropathic pain and the prophylaxis of headache (both tension and migraine)
- lofepramine has a lower incidence of toxicity in overdose
- amitriptyline and dosulepin (dothiepin) are considered the most dangerous in overdose
-

| More sedative | Less sedative |
|---|---|
| Amitriptyline<br>Clomipramine<br>Dosulepin<br>Trazodone* | Imipramine<br>Lofepramine<br>Nortriptyline |

*trazodone is technically a 'tricyclic-related antidepressant'

# ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy is a useful treatment option for patients with severe depression refractory to medication (e.g. catatonia) those with psychotic symptoms. The only absolute contraindications is raised intracranial pressure.

Short-term side-effects

- headache
- nausea
- short term memory impairment
- memory loss of events prior to ECT
- cardiac arrhythmia

Long-term side-effects

- some patients report impaired memory

# MONOAMINE OXIDASE INHIBITORS

Overview

- serotonin and noradrenaline are metabolised by monoamine oxidase in the presynaptic cell

Non-selective monoamine oxidase inhibitors

- e.g. tranylcypromine, phenelzine
- used in the treatment of atypical depression (e.g. hyperphagia) and other psychiatric disorder
- not used frequently due to side-effects

Adverse effects of non-selective monoamine oxidase inhibitors

- hypertensive reactions with tyramine containing foods e.g. cheese, pickled herring, Bovril, Oxo, Marmite, broad beans
- anticholinergic effects

# GENERALISED ANXIETY DISORDER

Management
- SSRI anti-depressants
- buspirone (5-HT1A partial agonist)
- beta-blockers
- benzodiazepines: use longer acting preparations e.g. diazepam, clonazepam
- cognitive behaviour therapy

# GENERALISED ANXIETY DISORDER AND PANIC DISORDER

Anxiety is a common disorder that can present in multiple ways. NICE define the central feature as an 'excessive worry about a number of different events associated with heightened tension.'

Always look for a potential physical cause when considering a psychiatric diagnosis. In anxiety disorders, important alternative causes include hyperthyroidism, cardiac disease and medication-induced anxiety (NICE). Medications that may trigger anxiety include salbutamol, theophylline, corticosteroids, antidepressants and caffeine

**Management of generalised anxiety disorder (GAD)**

NICE suggest a step-wise approach:
- step 1: education about GAD + active monitoring
- step 2: low intensity psychological interventions (individual non-facilitated self-help or individual guided self-help or psychoeducational groups)
- step 3: high intensity psychological interventions (cognitive behavioural therapy or applied relaxation) or drug treatment. See drug treatment below for more information
- step 4: highly specialist input e.g. Multi agency teams

Drug treatment
- NICE suggest sertraline should be considered the first-line SSRI
- interestingly for patients under the age of 30 years NICE recommend you warn patients of the increased risk of suicidal thinking and self-harm. Weekly follow-up is recommended for the first month

**Management of panic disorder**

Again a stepwise approach:

- step 1: recognition and diagnosis
- step 2: treatment in primary care - see below
- step 3: review and consideration of alternative treatments
- step 4: review and referral to specialist mental health services
- step 5: care in specialist mental health services

Treatment in primary care

- NICE recommend either cognitive behavioural therapy or drug treatment
- SSRIs are first-line. If contraindicated or no response after 12 weeks then imipramine or clomipramine should be offered

## GRIEF REACTION

It is normal for people to feel sadness and grief following the death of a loved one and this does not necessarily need to be medicalised. However, having some understanding of the potential stages a person may go through whilst grieving can help determine whether a patient is having a 'normal' grief reaction or is developing a more significant problem.

One of the most popular models of grief divides it into 5 stages.

- Denial: this may include a feeling of numbness and also pseudohallucinations of the deceased, both auditory and visual. Occasionally people may focus on physical objects that remind them of their loved one or even prepare meals for them
- Anger: this is commonly directed against other family members and medical professionals
- Bargaining
- Depression
- Acceptance

It should be noted that many patients will not go through all 5 stages.

Abnormal, or atypical, grief reactions are more likely to occur in women and if the death is sudden and unexpected. Other risk factors include a problematic relationship before death or if the patient has not much social support.

Features of atypical grief reactions include:

- delayed grief: sometimes said to occur when more than 2 weeks passes before grieving begins
- prolonged grief: difficult to define. Normal grief reactions may take up to and beyond 12 months

## SUICIDE: RISK FACTORS

The risk stratification of psychiatric patients into 'high', 'medium' or 'low risk' is common in clinical practice. Questions based on a patient's suicide risk are therefore often seen. However, it should be noted that there is a paucity of evidence addressing the positive predictive value of individual risk factors. An interesting review in the BMJ (BMJ 2017;359:j4627) concluded that 'there is no evidence that these assessments can usefully guide decision making' and noted that 50% of suicides occur in patients deemed 'low risk'.

Whilst the evidence base is relatively weak, there are a number of factors shown to be associated with an increased risk of suicide
- male sex (hazard ratio (HR) approximately 2.0)
- history of deliberate self-harm (HR 1.7)
- alcohol or drug misuse (HR 1.6)
- history of mental illness
  - depression
  - schizophrenia: NICE estimates that 10% of people with schizophrenia will complete suicide
- history of chronic disease
- advancing age
- unemployment or social isolation/living alone
- being unmarried, divorced or widowed

If a patient has actually attempted suicide, there are a number of factors associated with an increased risk of completed suicide at a future date:
- efforts to avoid discovery
- planning
- leaving a written note
- final acts such as sorting out finances
- violent method

**Protective factors**
There are, of course, factors which reduce the risk of a patient committing suicide. These include
- family support
- having children at home
- religious belief

# OCD

Pathophysiology
- some research suggest childhood group A beta-haemolytic streptococcal infection may have a role

Associations
- depression (30%)
- schizophrenia (3%)
- Sydenham's chorea
- Tourette's syndrome
- anorexia nervosa

# SCHIZOPHRENIA: EPIDEMIOLOGY

The strongest risk factor for developing a psychotic disorder (including schizophrenia) is family history. Having a parent with schizophrenia leads to a relative risk (RR) of 7.5.

Risk of developing schizophrenia
- monozygotic twin has schizophrenia = 50%
- parent has schizophrenia = 10-15%
- sibling has schizophrenia = 10%
- no relatives with schizophrenia = 1%

Other selected risk factors for psychotic disorders include:
- Black Caribbean ethnicity - RR 5.4
- Migration - RR 2.9
- Urban environment- RR 2.4
- Cannabis use - RR 1.4

# SCHIZOPHRENIA: FEATURES

Schneider's first rank symptoms may be divided into auditory hallucinations, thought disorders, passivity phenomena and delusional perceptions:

Auditory hallucinations of a specific type:
- two or more voices discussing the patient in the third person
- thought echo
- voices commenting on the patient's behaviour

Thought disorder*:
- thought insertion
- thought withdrawal
- thought broadcasting

Passivity phenomena:
- bodily sensations being controlled by external influence
- actions/impulses/feelings - experiences which are imposed on the individual or influenced by others

Delusional perceptions
- a two stage process) where first a normal object is perceived then secondly there is a sudden intense delusional insight into the objects meaning for the patient e.g. 'The traffic light is green therefore I am the King'.

Other features of schizophrenia include
- impaired insight
- incongruity/blunting of affect (inappropriate emotion for circumstances)
- decreased speech
- neologisms: made-up words
- catatonia
- negative symptoms: incongruity/blunting of affect, anhedonia (inability to derive pleasure), alogia (poverty of speech), avolition (poor motivation)

*occasionally referred to as thought alienation

## SCHIZOPHRENIA: MANAGEMENT

NICE published guidelines on the management of schizophrenia in 2009.

Key points:
- oral atypical antipsychotics are first-line
- cognitive behavioural therapy should be offered to all patients
- close attention should be paid to cardiovascular risk-factor modification due to the high rates of cardiovascular disease in schizophrenic patients (linked to antipsychotic medication and high smoking rates)

## SCHIZOPHRENIA: PROGNOSTIC INDICATORS

Factors associated with poor prognosis
- strong family history
- gradual onset
- low IQ
- premorbid history of social withdrawal
- lack of obvious precipitant

## ANTIPSYCHOTICS

Antipsychotics act as dopamine D2 receptor antagonists, blocking dopaminergic transmission in the mesolimbic pathways. Conventional antipsychotics are associated with problematic extrapyramidal side-effects which has led to the development of atypical antipsychotics such as clozapine

Extrapyramidal side-effects (EPSEs)

- Parkinsonism
- acute dystonia: sustained muscle contraction (e.g. torticollis, oculogyric crisis)
- akathisia (severe restlessness)
- tardive dyskinesia (late onset of choreoathetoid movements, abnormal, involuntary, may occur in 40% of patients, may be irreversible, most common is chewing and pouting of jaw)
- EPSEs may be managed with procyclidine

The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in elderly patients:
- increased risk of stroke
- increased risk of venous thromboembolism

Other side-effects
- antimuscarinic: dry mouth, blurred vision, urinary retention, constipation
- sedation, weight gain
- raised prolactin
  - may result in galactorrhoea
  - due to inhibition of the dopaminergic tuberoinfundibular pathway
- impaired glucose tolerance
- neuroleptic malignant syndrome: pyrexia, muscle stiffness
- reduced seizure threshold (greater with atypicals)
- prolonged QT interval (particularly haloperidol)

# ATYPICAL ANTIPSYCHOTICS

Atypical antipsychotics should now be used first-line in patients with schizophrenia, according to 2005 NICE guidelines. The main advantage of the atypical agents is a significant reduction in extrapyramidal side-effects.

Adverse effects of atypical antipsychotics
- weight gain
- clozapine is associated with agranulocytosis (see below)
- hyperprolactinaemia

The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in elderly patients:
- increased risk of stroke
- increased risk of venous thromboembolism

Examples of atypical antipsychotics
- clozapine
- olanzapine: higher risk of dyslipidemia and obesity

- risperidone
- quetiapine
- amisulpride
- aripiprazole: generally good side-effect profile, particularly for prolactin elevation

**Clozapine**

Clozapine, one of the first atypical agents to be developed, carries a significant risk of agranulocytosis and full blood count monitoring is therefore essential during treatment. For this reason, clozapine should only be used in patients resistant to other antipsychotic medication. The BNF states:

*Clozapine should be introduced if schizophrenia is not controlled despite the sequential use of two or more antipsychotic drugs (one of which should be a second-generation antipsychotic drug), each for at least 6–8 weeks.*

Adverse effects of clozapine

- agranulocytosis (1%), neutropaenia (3%)
- reduced seizure threshold - can induce seizures in up to 3% of patients
- constipation
- myocarditis: a baseline ECG should be taken before starting treatment
- hypersalivation

Dose adjustment of clozapine might be necessary if smoking is started or stopped during treatment.

# HYPOMANIA VS. MANIA

| Mania | Hypomania |
|---|---|
| • Lasts for at least 7 days - Causes severe functional impairment in social and work setting<br>• May require hospitalization due to risk of harm to self or others<br>• May present with **psychotic symptoms** | A lesser version of mania<br> Lasts for < 7 days, typically 3-4 days. Can be high functioning and does not impair functional capacity in social or work setting<br> Unlikely to require hospitalization<br> Does not exhibit any psychotic symptoms |

Therefore, the length of symptoms, severity and presence of psychotic symptoms (e.g. delusions of grandeur, auditory hallucinations) helps differentiates mania from hypomania.

The following symptoms are common to both hypomania and mania

Mood
- predominately elevated
- irritable

Speech and thought
- pressured
- flight of ideas: characterised by rapid speech with frequent changes in topic based on associations, distractions or word play
- poor attention

Behaviour
- insomnia
- loss of inhibitions: sexual promiscuity, overspending, risk-taking
- increased appetite

# LITHIUM

Lithium is mood stabilising drug used most commonly prophylactically in bipolar disorder but also as an adjunct in refractory depression. It has a very narrow therapeutic range (0.4-1.0 mmol/L) and a long plasma half-life being excreted primarily by the kidneys.

Mechanism of action - not fully understood, two theories:
- interferes with inositol triphosphate formation
- interferes with cAMP formation

Adverse effects

- nausea/vomiting, diarrhoea
- fine tremor
- nephrotoxicity: polyuria, secondary to nephrogenic diabetes insipidus
- thyroid enlargement, may lead to hypothyroidism
- ECG: T wave flattening/inversion
- weight gain
- idiopathic intracranial hypertension
- leucocytosis
- hyperparathyroidism and resultant hypercalcaemia

Monitoring of patients on lithium therapy

- inadequate monitoring of patients taking lithium is common - NICE and the National Patient Safety Agency (NPSA) have issued guidance to try and address this. As a result it is often an exam hot topic
- after starting lithium levels should be performed weekly and after each dose change until concentrations are stable
- once established, lithium blood level should 'normally' be checked every 3 months
- after a change in dose, lithium levels should be taken a week later and 12 hours after the last dose
- thyroid and renal function should be checked every 6 months
- patients should be issued with an information booklet, alert card and record book

# PERSONALITY DISORDERS

| Disorder | Features |
|---|---|
| Antisocial | • Failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest;<br>• More common in men;<br>• Deception, as indicated by repeatedly lying, use of aliases, or conning others for personal profit or pleasure;<br>• Impulsiveness or failure to plan ahead;<br>• Irritability and aggressiveness, as indicated by repeated physical fights or assaults;<br>• Reckless disregard for safety of self or others;<br>• Consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations;<br>• Lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another |
| Avoidant | • Avoidance of occupational activities which involve significant interpersonal contact due to fears of criticism, or rejection.<br>• Unwillingness to be involved unless certain of being liked<br>• Preoccupied with ideas that they are being criticised or rejected in social situations<br>• Restraint in intimate relationships due to the fear of being ridiculed<br>• Reluctance to take personal risks doe to fears of embarrassment<br>• Views self as inept and inferior to others<br>• Social isolation accompanied by a craving for social contact |
| Borderline | • Efforts to avoid real or imagined abandonment<br>• Unstable interpersonal relationships which alternate between idealization and devaluation<br>• Unstable self image<br>• Impulsivity in potentially self damaging area (e.g. Spending, sex, substance abuse)<br>• Recurrent suicidal behaviour<br>• Affective instability<br>• Chronic feelings of emptiness<br>• Difficulty controlling temper<br>• Quasi psychotic thoughts |
| Dependent | • Difficulty making everyday decisions without excessive reassurance from others<br>• Need for others to assume responsibility for major areas of their life<br>• Difficulty in expressing disagreement with others due to fears of losing support<br>• Lack of initiative<br>• Unrealistic fears of being left to care for themselves<br>• Urgent search for another relationship as a source of care and support when a close relationship ends<br>• Extensive efforts to obtain support from others |

| Disorder | Features |
|---|---|
|  | • Unrealistic feelings that they cannot care for themselves |
| Histrionic | • Inappropriate sexual seductiveness<br>• Need to be the centre of attention<br>• Rapidly shifting and shallow expression of emotions<br>• Suggestibility<br>• Physical appearance used for attention seeking purposes<br>• Impressionistic speech lacking detail<br>• Self dramatization<br>• Relationships considered to be more intimate than they are |
| Narcissistic | • Grandiose sense of self importance<br>• Preoccupation with fantasies of unlimited success, power, or beauty<br>• Sense of entitlement<br>• Taking advantage of others to achieve own needs<br>• Lack of empathy<br>• Excessive need for admiration<br>• Chronic envy<br>• Arrogant and haughty attitude |
| Obsessive-compulsive | • Is occupied with details, rules, lists, order, organization, or agenda to the point that the key part of the activity is gone<br>• Demonstrates perfectionism that hampers with completing tasks<br>• Is extremely dedicated to work and efficiency to the elimination of spare time activities<br>• Is meticulous, scrupulous, and rigid about etiquettes of morality, ethics, or values<br>• Is not capable of disposing worn out or insignificant things even when they have no sentimental meaning<br>• Is unwilling to pass on tasks or work with others except if they surrender to exactly their way of doing things<br>• Takes on a stingy spending style towards self and others; and shows stiffness and stubbornness |
| Paranoid | • Hypersensitivity and an unforgiving attitude when insulted<br>• Unwarranted tendency to questions the loyalty of friends<br>• Reluctance to confide in others<br>• Preoccupation with conspirational beliefs and hidden meaning<br>• Unwarranted tendency to perceive attacks on their character |
| Schizoid | • Indifference to praise and criticism<br>• Preference for solitary activities<br>• Lack of interest in sexual interactions<br>• Lack of desire for companionship<br>• Emotional coldness<br>• Few interests |

| Disorder | Features |
|---|---|
|  | • Few friends or confidants other than family |
| Schizotypal | • Ideas of reference (differ from delusions in that some insight is retained)<br>• Odd beliefs and magical thinking<br>• Unusual perceptual disturbances<br>• Paranoid ideation and suspiciousness<br>• Odd, eccentric behaviour<br>• Lack of close friends other than family members<br>• Inappropriate affect<br>• Odd speech without being incoherent |

Management

- PDs are often thought to be 'untreatable' by definition
- however, a number of approaches have been shown to help patients, including:
  - psychological therapies: dialectical behaviour therapy

# BULIMIA NERVOSA

Bulimia nervosa is a type of eating disorder characterised by episodes of binge eating followed by intentional vomiting or other purgative behaviours such as the use of laxatives or diuretics or exercising.

DSM 5 diagnostic criteria for a diagnosis of bulimia nervosa:
- recurrent episodes of binge eating (eating an amount of food that is definitely larger than most people would eat during a similar period of time and circumstances)
- a sense of lack of control over eating during the episode
- recurrent inappropriate compensatory behaviour in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, or other medications, fasting, or excessive exercise.
- the binge eating and compensatory behaviours both occur, on average, at least once a week for three months.
- self-evaluation is unduly influenced by body shape and weight.
- the disturbance does not occur exclusively during episodes of anorexia nervosa.

Management
- referral for specialist care is appropriate in all cases
- NICE recommend bulimia-nervosa-focused guided self-help for adults
- If bulimia-nervosa-focused guided self-help is unacceptable, contraindicated, or ineffective after 4 weeks of treatment, NICE recommend that we consider individual eating-disorder-focused cognitive behavioural therapy (CBT-ED)
- children should be offered bulimia-nervosa-focused family therapy (FT-BN)
- pharmacological treatments have a limited role - a trial of high-dose fluoxetine is currently licensed for bulimia but long-term data is lacking

# ANOREXIA NERVOSA: FEATURES

Anorexia nervosa is associated with a number of characteristic clinical signs and physiological abnormalities which are summarised below

Features
- reduced body mass index
- bradycardia
- hypotension
- enlarged salivary glands

Physiological abnormalities
- hypokalaemia

- low FSH, LH, oestrogens and testosterone
- raised cortisol and growth hormone
- impaired glucose tolerance
- hypercholesterolaemia
- hypercarotinaemia
- low T3

# POST-PARTUM MENTAL HEALTH PROBLEMS

Post-partum mental health problems range from the 'baby-blues' to puerperal psychosis.

The **Edinburgh Postnatal Depression Scale** may be used to screen for depression:
10-item questionnaire, with a maximum score of 30
indicates how the mother has felt over the previous week
score > 13 indicates a 'depressive illness of varying severity'
sensitivity and specificity > 90%
includes a question about self-harm

| 'Baby-blues' | Postnatal depression | Puerperal psychosis |
|---|---|---|
| Seen in around 60-70% of women<br>Typically seen 3-7 days following birth and is more common in primips<br>Mothers are characteristically anxious, tearful and irritable | Affects around 10% of women<br>Most cases start within a month and typically peaks at 3 months<br>Features are similar to depression seen in other circumstances | Affects approximately 0.2% of women<br>Onset usually within the first 2-3 weeks following birth<br>Features include severe swings in mood (similar to bipolar disorder) and disordered perception (e.g. auditory hallucinations) |
| Reassurance and support, the health visitor has a key role | As with the baby blues reassurance and support are important<br>Cognitive behavioural therapy may be beneficial. Certain SSRIs such as sertraline and paroxetine* may be used if symptoms are severe** - whilst they are secreted in breast milk it is not thought to be harmful to the infant | Admission to hospital is usually required<br>There is around a 25-50% risk of recurrence following future pregnancies |

# POST-TRAUMATIC STRESS DISORDER

Post-traumatic stress disorder (PTSD) can develop in people of any age following a traumatic event, for example, a major disaster or childhood sexual abuse. It encompasses what became known as 'shell shock' following the first world war. One of the DSM-IV diagnostic criteria is that symptoms have been present for more than one month.

Features

- re-experiencing: flashbacks, nightmares, repetitive and distressing intrusive images
- avoidance: avoiding people, situations or circumstances resembling or associated with the event
- hyperarousal: hypervigilance for threat, exaggerated startle response, sleep problems, irritability and difficulty concentrating
- emotional numbing - lack of ability to experience feelings, feeling detached

from other people

- depression
- drug or alcohol misuse
- anger
- unexplained physical symptoms

Management

- following a traumatic event single-session interventions (often referred to as debriefing) are not recommended
- watchful waiting may be used for mild symptoms lasting less than 4 weeks
- military personnel have access to treatment provided by the armed forces
- trauma-focused cognitive behavioural therapy (CBT) or eye movement desensitisation and reprocessing (EMDR) therapy may be used in more severe cases
- drug treatments for PTSD should not be used as a routine first-line treatment for adults. If drug treatment is used then venlafaxine or a selective serotonin reuptake inhibitor (SSRI), such as sertraline should be tried. In severe cases, NICE recommends that risperidone may be used

# ALCOHOL WITHDRAWAL

Mechanism

- chronic alcohol consumption enhances GABA mediated inhibition in the CNS (similar to benzodiazepines) and inhibits NMDA-type glutamate receptors
- alcohol withdrawal is thought to be lead to the opposite (decreased inhibitory GABA and increased NMDA glutamate transmission)

Features

- symptoms start at 6-12 hours: tremor, sweating, tachycardia, anxiety
- peak incidence of seizures at 36 hours
- peak incidence of delirium tremens is at 48-72 hours: coarse tremor, confusion, delusions, auditory and visual hallucinations, fever, tachycardia

Management

- patients with a history of complex withdrawals from alcohol (i.e. delirium tremens, seizures, blackouts) should be admitted to hospital for monitoring until withdrawals stabilised
- first-line: benzodiazepines e.g. chlordiazepoxide. Lorazepam may be preferable in patients with hepatic failure. Typically given as part of a reducing dose protocol
- carbamazepine also effective in treatment of alcohol withdrawal
- phenytoin is said not to be as effective in the treatment of alcohol withdrawal seizures

*paroxetine is recommended by SIGN because of the low milk/plasma ratio
**fluoxetine is best avoided due to a long half-life

# KORSAKOFF'S SYNDROME

Overview

- marked memory disorder often seen in alcoholics
- thiamine deficiency causes damage and haemorrhage to the mammillary bodies of the hypothalamus and the medial thalamus
- in often follows on from untreated Wernicke's encephalopathy

Features

- anterograde amnesia: inability to acquire new memories
- retrograde amnesia
- confabulation

# Relationship between Wernicke's encephalopathy and Korsakoff's syndrome

Wernicke's encephalopathy

- nystagmus
- ophthalmoplegia
- ataxia

→ if untreated → + Korsakoff's syndrome

- amnesia (antero + retrograde
- confabulation

i.e. initially
↳ Wernicke's encephalopathy
if not treated with thiamine
↳ Wernicke-Korsakoff syndrome

# SLEEP PARALYSIS

Sleep paralysis is a common condition characterized by transient paralysis of skeletal muscles which occurs when awakening from sleep or less often while falling asleep. It is thought to be related to the paralysis that occurs as a natural part of REM (rapid eye movement) sleep. Sleep paralysis is recognised in a wide variety of cultures

Features
- paralysis - this occurs after waking up or shortly before falling asleep
- hallucinations - images or speaking that appear during the paralysis

Management
- if troublesome clonazepam may be used

# POST-CONCUSSION SYNDROME

Post-concussion syndrome is seen after even minor head trauma

Typical features include
- headache
- fatigue
- anxiety/depression
- dizziness

# CHARLES-BONNET SYNDROME

Charles-Bonnet syndrome (CBS) is characterised by persistent or recurrent complex hallucinations (usually visual or auditory), occurring in clear consciousness. This is generally against a background of visual impairment (although visual impairment is not mandatory for a diagnosis). Insight is usually preserved. This must occur in the absence of any other significant neuropsychiatric disturbance.

Risk factors include:
- Advanced age
- Peripheral visual impairment
- Social isolation
- Sensory deprivation
- Early cognitive impairment

CBS is equally distributed between sexes and does not show any familial predisposition. The most common ophthalmological conditions associated with this syndrome are age-related macular degeneration, followed by glaucoma and cataract.

Well-formed complex visual hallucinations are thought to occur in 10-30 per cent of individuals with severe visual impairment. Prevalence of CBS in visually impaired people is thought to be between 11 and 15 per cent.

Around a third find the hallucinations themselves an unpleasant or disturbing experience. In a large study published in the British Journal of Ophthalmology, 88% had CBS for 2 years or more, resolving in only 25% at 9 years (thus it is not generally a transient experience).

*Cox (2014) Negative outcome Charles Bonnet Syndrome. Br J Ophthalmol.*

## BODY DYSMORPHIC DISORDER

Body dysmorphic disorder (sometimes referred to as dysmorphophobia) is a mental disorder where patients have a significantly distorted body image

Diagnostic and Statistical Manual (DSM) IV criteria:
- Preoccupation with an imagine defect in appearance. If a slight physical anomaly is present, the person's concern is markedly excessive
- The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
- The preoccupation is not better accounted for by another mental disorder (e.g., dissatisfaction with body shape and size in Anorexia Nervosa)

## COTARD SYNDROME

Cotard syndrome is a rare mental disorder where the affected patient believes that they (or in some cases just a part of their body) is either dead or non-existent. This delusion is often difficult to treat and can result in significant problems due to patients stopping eating or drinking as they deem it not necessary.

Cotard syndrome is associated with severe depression and psychotic disorders.

## DE CLERAMBAULT'S SYNDROME

De Clerambault's syndrome, also known as erotomania, is a form of paranoid delusion with an amorous quality. The patient, often a single woman, believes that a famous person is in love with her.

# OTHELLO'S SYNDROME

Othello's syndrome is pathological jealousy where a person is convinced their partner is cheating on them without any real proof. This is accompanied by socially unacceptable behaviour linked to these claims.

# AGORAPHOBIA

Agoraphobia is primarily describes a fear of open spaces but also includes related aspects, e.g. the presence of crowds or the difficulty of escaping to a safe place

# APHONIA

Aphonia describes the inability to speak. Causes include:
- recurrent laryngeal nerve palsy (e.g. Post-thyroidectomy)
- psychogenic

# UNEXPLAINED SYMPTOMS

There are a wide variety of psychiatric terms for patients who have symptoms for which no organic cause can be found:

Somatisation disorder
- multiple physical SYMPTOMS present for at least 2 years
- patient refuses to accept reassurance or negative test results

Hypochondrial disorder
- persistent belief in the presence of an underlying serious DISEASE, e.g. cancer
- patient again refuses to accept reassurance or negative test results

Conversion disorder
- typically involves loss of motor or sensory function
- the patient doesn't consciously feign the symptoms (factitious disorder) or seek material gain (malingering)
- patients may be indifferent to their apparent disorder - la belle indifference - although this has not been backed up by some studies

Dissociative disorder
- dissociation is a process of 'separating off' certain memories from normal consciousness

- in contrast to conversion disorder involves psychiatric symptoms e.g. Amnesia, fugue, stupor
- dissociative identity disorder (DID) is the new term for multiple personality disorder as is the most severe form of dissociative disorder

Factitious disorder

- also known as Munchausen's syndrome
- the intentional production of physical or psychological symptoms

Malingering

- fraudulent simulation or exaggeration of symptoms with the intention of financial or other gain

# PASSMEDICINE NOTES
# GERIATRIC MEDICINE

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# ACUTE CONFUSIONAL STATE

Acute confusional state is also known as delirium or acute organic brain syndrome. It affects up to 30% of elderly patients admitted to hospital.

Predisposing factors include:
- age > 65 years
- background of dementia
- significant injury e.g. hip fracture
- frailty or multimorbidity
- polypharmacy

The precipitating events are often multifactorial and may include:
- infection: particularly urinary tract infections
- metabolic: e.g. hypercalcaemia, hypoglycaemia, hyperglycaemia, dehydration
- change of environment
- any significant cardiovascular, respiratory, neurological or endocrine condition
- severe pain
- alcohol withdrawal
- constipation

Features - a wide variety of presentations
- memory disturbances (loss of short term > long term)
- may be very agitated or withdrawn
- disorientation
- mood change
- visual hallucinations
- disturbed sleep cycle
- poor attention

Management
- treatment of the underlying cause
- modification of the environment
- the 2006 Royal College of Physicians publication 'The prevention, diagnosis and management of delirium in older people: concise guidelines' recommended haloperidol 0.5 mg as the first-line sedative
- the 2010 NICE delirium guidelines advocate the use of haloperidol or olanzapine

# DELIRIUM VS. DEMENTIA

Factors favouring delirium over dementia

- impairment of consciousness
- fluctuation of symptoms: worse at night, periods of normality
- abnormal perception (e.g. illusions and hallucinations)
- agitation, fear
- delusions

# DEMENTIA

Dementia is thought to affect over 700,000 people in the UK and accounts for a large amount of health and social care spending. The most common cause of dementia in the UK is Alzheimer's disease followed by vascular and Lewy body dementia. These conditions may coexist.

Features

- diagnosis can be difficult and is often delayed
- assessment tools recommended by NICE for the non-specialist setting include: 10-point cognitive screener (10-CS), 6-Item cognitive impairment test (6CIT)
- assessment tools **not** recommended by NICE for the non-specialist setting include the abbreviated mental test score (AMTS), General practitioner assessment of cognition (GPCOG) and the mini-mental state examination (MMSE) have been widely used. A MMSE score of 24 or less out of 30 suggests dementia

Management

- in primary care, a blood screen is usually sent to exclude reversible causes (e.g. Hypothyroidism). NICE recommend the following tests: FBC, U&E, LFTs, calcium, glucose, TFTs, vitamin B12 and folate levels. Patients are now commonly referred on to old-age psychiatrists (sometimes working in 'memory clinics').
- in secondary care, neuroimaging is performed* to exclude other reversible conditions (e.g. Subdural haematoma, normal pressure hydrocephalus) and help provide information on aetiology to guide prognosis and management

*in the 2011 NICE guidelines structural imaging was said to be essential in the investigation of dementia

# DEMENTIA: CAUSES

Common causes
Alzheimer's disease

- cerebrovascular disease: multi-infarct dementia (c. 10-20%)
- Lewy body dementia (c. 10-20%)

Rarer causes (c. 5% of cases)
- Huntington's
- CJD
- Pick's disease (atrophy of frontal and temporal lobes)
- HIV (50% of AIDS patients)

Important differentials, potentially treatable
- hypothyroidism, Addison's
- B12/folate/thiamine deficiency
- syphilis
- brain tumour
- normal pressure hydrocephalus
- subdural haematoma
- depression
- chronic drug use e.g. Alcohol, barbiturates

# ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive degenerative disease of the brain accounting for the majority of dementia seen in the UK.

Genetics
- most cases are sporadic
- 5% of cases are inherited as an autosomal dominant trait
- mutations in the amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14) and presenilin 2 (chromosome 1) genes are thought to cause the inherited form
- apoprotein E allele E4 - encodes a cholesterol transport protein
- risk factors include Down's syndrome

Pathological changes
- macroscopic: widespread cerebral atrophy, particularly involving the cortex and hippocampus
- microscopic: cortical plaques due to deposition of type A-Beta-amyloid protein and intraneuronal neurofibrillary tangles caused by abnormal aggregation of the tau protein. Hyperphosphorylation of the tau protein has been linked to AD
- biochemical: there is a deficit of acetylcholine from damage to an ascending forebrain projection

Neurofibrillary tangles
- paired helical filaments are partly made from a protein called tau

- tau is a protein that interacts with tubulin to stabilize microtubules and promote tubulin assembly into microtubules
- in AD are tau proteins are excessively phosphorylated, impairing the function

## ALZHEIMER'S DISEASE: MANAGEMENT

Alzheimer's disease is a progressive degenerative disease of the brain accounting for the majority of dementia seen in the UK

Non-pharmacological management
- NICE recommend offering 'a range of activities to promote wellbeing that are tailored to the person's preference'
- NICE recommend offering group cognitive stimulation therapy for patients with mild and moderate dementia
- other options to consider include group reminiscence therapy and cognitive rehabilitation

Pharmacological management
- NICE updated it's dementia guidelines in 2018
- the three acetylcholinesterase inhibitors (donepezil, galantamine and rivastigmine) as options for managing mild to moderate Alzheimer's disease
- memantine (an NMDA receptor antagonist) is in simple terms the 'second-line' treatment for Alzheimer's, NICE recommend it is used in the following situation reserved for patients with
- → moderate Alzheimer's who are intolerant of, or have a contraindication to, acetylcholinesterase inhibitors
- → as an add-on drug to acetylcholinesterase inhibitors for patients with moderate or severe Alzheimer's
- → monotherapy in severe Alzheimer's

Managing non-cognitive symptoms
- NICE does not recommend antidepressants for mild to moderate depression in patients with dementia
- antipsychotics should only be used for patients at risk of harming themselves or others, or when the agitation, hallucinations or delusions are causing them severe distress

Donepezil
- is relatively contraindicated in patients with bradycardia
- adverse effects include insomnia

# LEWY BODY DEMENTIA

Lewy body dementia is an increasingly recognised cause of dementia, accounting for up to 20% of cases. The characteristic pathological feature is alpha-synuclein cytoplasmic inclusions (Lewy bodies) in the substantia nigra, paralimbic and neocortical areas.

The relationship between Parkinson's disease and Lewy body dementia is complicated, particularly as dementia is often seen in Parkinson's disease. Also, up to 40% of patients with Alzheimer's have Lewy bodies.

Features

- progressive cognitive impairment
    - in contrast to Alzheimer's, early impairments in attention and executive function rather than just memory loss
    - cognition may be fluctuating, in contrast to other forms of dementia
    - usually develops before parkinsonism
- parkinsonism
- visual hallucinations (other features such as delusions and non-visual hallucinations may also be seen)

Diagnosis

- usually clinical
- single-photon emission computed tomography (SPECT) is increasingly used. It is currently commercially known as a DaTscan. Dopaminergic iodine-123-radiolabelled 2-carbomethoxy-3-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (123-I FP-CIT) is used as the radioisotope. The sensitivity of SPECT in diagnosing Lewy body dementia is around 90% with a specificity of 100%

Management

- both acetylcholinesterase inhibitors (e.g. donepezil, rivastigmine) and memantine can be used as they are in Alzheimer's. NICE have made detailed recommendations about what drugs to use at what stages. Please see the link for more details
- neuroleptics should be avoided in Lewy body dementia as patients are extremely sensitive and may develop irreversible parkinsonism. Questions may give a history of a patient who has deteriorated following the introduction of an antipsychotic agent

# FRONTOTEMPORAL LOBAR DEGENERATION

Frontotemporal lobar degeneration (FTLD) is the third most common type of cortical dementia after Alzheimer's and Lewy body dementia.

There are three recognised types of FTLD
- Frontotemporal dementia (Pick's disease)
- Progressive non fluent aphasia (chronic progressive aphasia, CPA)
- Semantic dementia

| Common features of frontotemporal lobar dementias |
|---|
| Onset before 65 |
| Insidious onset |
| Relatively preserved memory and visuospatial skills |
| Personality change and social conduct problems |

**Pick's disease**

This is the most common type and is characterised by personality change and impaired social conduct. Other common features include hyperorality, disinhibition, increased appetite, and perseveration behaviours.

Focal gyral atrophy with a knife-blade appearance is characteristic of Pick's disease.

Macroscopic changes seen in Pick's disease include:-
- Atrophy of the frontal and temporal lobes

Microscopic changes include:-
- Pick bodies - spherical aggregations of tau protein (silver-staining)
- Gliosis
- Neurofibrillary tangles
- Senile plaques

Management
- NICE do not recommend that AChE inhibitors or memantine are used in people with frontotemporal dementia

**CPA**

Here the chief factor is non fluent speech. They make short utterances that are agrammatic. Comprehension is relatively preserved.

**Semantic dementia**

Here the patient has a fluent progressive aphasia. The speech is fluent but empty and conveys little meaning. Unlike in Alzheimer's memory is better for recent rather than remote events.

# VASCULAR DEMENTIA

Vascular dementia (VD) is the second most common form of dementia after Alzheimer disease. It is not a single disease but a group of syndromes of cognitive impairment caused by different mechanisms causing ischaemia or haemorrhage secondary to cerebrovascular disease. Vascular dementia has been increasingly recognised as the most severe form of the spectrum of deficits encompassed by the term vascular cognitive impairment (VCI). Early detection and an accurate diagnosis are important in the prevention of vascular dementia.

Epidemiology

- VD is thought to account for around 17% of dementia in the UK
- Prevalence of dementia following a first stroke varies depending on location and size of the infarct, definition of dementia, interval after stroke and age among other variables. Overall, stroke doubles the risk of developing dementia.
- Incidence increases with age

The main subtypes of VD:

- Stroke-related VD – multi-infarct or single-infarct dementia
- Subcortical VD – caused by small vessel disease
- Mixed dementia – the presence of both VD and Alzheimer's disease

Risk factors

- History of stroke or transient ischaemic attack (TIA)
- Atrial fibrillation
- Hypertension
- Diabetes mellitus
- Hyperlipidaemia
- Smoking
- Obesity
- Coronary heart disease
- A family history of stroke or cardiovascular

Rarely, VD can be inherited as in the case of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Patients with VD typically presents with

- Several months or several years of a history of a sudden or **stepwise deterioration** of cognitive function.

Symptoms and the speed of progression vary but may include:

- Focal neurological abnormalities e.g. visual disturbance, sensory or motor symptoms
- The difficulty with attention and concentration
- Seizures

- Memory disturbance
- Gait disturbance
- Speech disturbance
- Emotional disturbance

Diagnosis is made based on:
- A comprehensive history and physical examination
- Formal screen for cognitive impairment
- Medical review to exclude medication cause of cognitive decline
- MRI scan – may show infarcts and extensive white matter changes

National Institute for health and care excellence (NICE) recommends that diagnosis be made using the NINDS-AIREN criteria for probable vascular dementia

| |
|---|
| Presence of cognitive decline that interferes with activities of daily living, not due to secondary effects of the cerebrovascular event<br>• established using clinical examination and neuropsychological testing |
| Cerebrovascular disease<br>• defined by neurological signs and/or brain imaging |
| A relationship between the above two disorders inferred by:<br>• the onset of dementia within three months following a recognised stroke<br>• an abrupt deterioration in cognitive functions<br>• fluctuating, stepwise progression of cognitive deficits |

General management
- Treatment is mainly symptomatic with the aim to address individual problems and provide support to the patient and carers
- Important to detect and address cardiovascular risk factors – for slowing down the progression

Non-pharmacological management
- Tailored to the individual
- Include: cognitive stimulation programmes, multisensory stimulation, music and art therapy, animal-assisted therapy
- Managing challenging behaviours e.g. address pain, avoid overcrowding, clear communication

Pharmacological management

- There is no specific pharmacological treatment approved for cognitive symptoms
- Only consider AChE inhibitors or memantine for people with vascular dementia if they have suspected comorbid Alzheimer’s disease, Parkinson’s disease dementia or dementia with Lewy bodies.
- There is no evidence that aspirin is effective in treating patients with a diagnosis of vascular dementia.
- No randomized trials found evaluating statins for vascular dementia

# PRESSURE ULCERS

The following is based on a 2009 NHS Best Practice Statement. Please see the link for further details. Some selected points are listed below. NICE also published guidelines in 2014.

Pressure ulcers develop in patients who are unable to move parts of their body due to illness, paralysis or advancing age. They typically develop over bony prominences such as the sacrum or heel. The following factors predispose to the development of pressure ulcers:
- malnourishment
- incontinence
- lack of mobility
- pain (leads to a reduction in mobility)

The **Waterlow** score is widely used to screen for patients who are at risk of developing pressure areas. It includes a number of factors including body mass index, nutritional status, skin type, mobility and continence.

Grading of pressure ulcers - the following is taken from the European Pressure Ulcer Advisory Panel classification system.

| Grade | Findings |
|---|---|
| **Grade 1** | Non-blanchable erythema of intact skin. Discolouration of the skin, warmth, oedema, induration or hardness may also be used as indicators, particularly on individuals with darker skin |
| **Grade 2** | Partial thickness skin loss involving epidermis or dermis, or both. The ulcer is superficial and presents clinically as an abrasion or blister |
| **Grade 3** | Full thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia. |
| **Grade 4** | Extensive destruction, tissue necrosis, or damage to muscle, bone or supporting structures with or without full thickness skin loss |

Management
- a moist wound environment encourages ulcer healing. Hydrocolloid dressings and hydrogels may help facilitate this. The use of soap should be discouraged to avoid drying the wound
- wound swabs should not be done routinely as the vast majority of pressure ulcers are colonised with bacteria. The decision to use systemic antibiotics should be taken on a clinical basis (e.g. Evidence of surrounding cellulitis)
- consider referral to the tissue viability nurse
- surgical debridement may be beneficial for selected wounds

# PASSMEDICINE NOTES PALLIATIVE MEDICINE & END OF LIFE CARE

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# PALLIATIVE CARE PRESCRIBING: PAIN

**NICE guidelines**
In 2012 NICE published guidelines on the use of opioids in palliative care. Selected points are listed below. Please see the link for more details.

Starting treatment
- when starting treatment, offer patients with advanced and progressive disease regular oral modified-release (MR) or oral immediate-release morphine (depending on patient preference), with oral immediate-release morphine for breakthrough pain
- if no comorbidities use 20-30mg of MR a day with 5mg morphine for breakthrough pain. For example, 15mg modified-release morphine tablets twice a day with 5mg of oral morphine solution as required
- oral modified-release morphine should be used in preference to transdermal patches
- laxatives should be prescribed for all patients initiating strong opioids
- patients should be advised that nausea is often transient. If it persists then an antiemetic should be offered
- drowsiness is usually transient - if it does not settle then adjustment of the dose should be considered

**SIGN guidelines**
SIGN issued guidance on the control of pain in adults with cancer in 2008. Selected points
- the breakthrough dose of morphine is one-sixth the daily dose of morphine
- all patients who receive opioids should be prescribed a laxative
- opioids should be used with caution in patients with chronic kidney disease
    - oxycodone is preferred to morphine in palliative patients with mild-moderate renal impairment
    - if renal impairment is more severe, alfentanil, buprenorphine and fentanyl are preferred
- metastatic bone pain may respond to strong opioids, bisphosphonates or radiotherapy. The assertion that NSAIDs are particularly effective for metastatic bone pain is not supported by studies. Strong opioids have the lowest number needed to treat for relieving the pain and can provide quick relief, in contrast to radiotherapy and bisphosphonates*. All patients, however, should be considered for referral to a clinical oncologist for consideration of further treatments such as radiotherapy

**Other points**
When increasing the dose of opioids the next dose should be increased by 30-50%.

In addition to strong opioids, bisphosphonates and radiotherapy, denosumab may be used to treat metastatic bone pain.

### Opioid side-effects

| Usually transient | Usually persistent |
|---|---|
| Nausea<br>Drowsiness | Constipation |

### Conversion between opioids

| From | To | Conversion factor |
|---|---|---|
| Oral codeine | Oral morphine | Divide by 10 |
| Oral tramadol | Oral morphine | Divide by 10** |

Oxycodone generally causes less sedation, vomiting and pruritis than morphine but more constipation.

| From | To | Conversion factor |
|---|---|---|
| Oral morphine | Oral oxycodone | Divide by 1.5-2*** |

The current BNF gives the following conversion factors for transdermal perparations
a transdermal fentanyl 12 microgram patch equates to approximately 30 mg oral morphine daily
a transdermal buprenorphine 10 microgram patch equates to approximately 24 mg oral morphine daily.

| From | To | Conversion factor |
|---|---|---|
| Oral morphine | Subcutaneous morphine | Divide by 2 |
| Oral morphine | Subcutaneous diamorphine | Divide by 3 |
| Oral oxycodone | Subcutaneous diamorphine | Divide by 1.5 |

*BMJ 2015;350:h315 Cancer induced bone pain

**this has previously been stated as 5 but the current version of the BNF states a conversion of 10

***historically a conversion factor of 2 has been used (i.e. oral oxycodone is twice as strong as oral morphine). The current BNF however uses a conversion rate of 1.5

# PALLIATIVE CARE PRESCRIBING: AGITATION AND CONFUSION

Underlying causes of confusion need to be looked for and treated as appropriate, for example hypercalcaemia, infection, urinary retention and medication. If specific treatments fail then the following may be tried:
- first choice: haloperidol
- other options: chlorpromazine, levomepromazine

In the terminal phase of the illness then agitation or restlessness is best treated with midazolam

# PALLIATIVE CARE PRESCRIBING: HICCUPS

Management of hiccups
- chlorpromazine is licensed for the treatment of intractable hiccups
- haloperidol, gabapentin are also used
- dexamethasone is also used, particularly if there are hepatic lesions

# PALLIATIVE CARE PRESCRIBING: SECRETIONS

These are common in the last days of life, but are generally more troubling for family members than for the patient themselves.

**Management**
Conservative:
- Avoiding fluid overload - particularly stopping IV or subcutaneous fluids
- Educating the family that the patient is likely not troubled by secretions

Medical:
- First-line: hyoscine butylbromide
- Second-line: glycopyrronium bromide

# SYRINGE DRIVERS

A syringe driver should be considered in the palliative care setting when a patient is unable to take oral medication due to nausea, dysphagia, intestinal obstruction, weakness or coma. In the UK there are two main types of syringe driver:

- Graseby MS16A (blue): the delivery rate is given in mm per hour
- Graseby MS26 (green): the delivery rate is given in mm per 24 hours

The majority of drugs are compatible with water for injection although for the following drugs sodium chloride 0.9% is recommended:

- granisetron
- ketamine
- ketorolac
- octreotide
- ondansetron

Commonly used drugs

- nausea and vomiting: cyclizine, levomepromazine, haloperidol, metoclopramide
- respiratory secretions: hyoscine hydrobromide
- bowel colic: hyoscine butylbromide
- agitation/restlessness: midazolam, haloperidol, levomepromazine
- pain: diamorphine is the preferred opioid

Mixing and compatibility issues

- diamorphine is compatible with the majority of other drugs used including cyclizine*, dexamethasone, haloperidol, hyoscine butylbromide, hyoscine hydrobromide, levomepromazine, metoclopramide, midazolam
- cyclizine is incompatible with a number of drugs including clonidine, dexamethasone, hyoscine butylbromide (occasional), ketamine, ketorolac, metoclopramide, midazolam, octreotide, sodium chloride 0.9%

*precipitation may be seen at higher doses

# PASSMEDICINE NOTES RHEUMATOLOGY

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# ROTATOR CUFF MUSCLES

**SItS** - small t for teres minor

**S**upraspinatus
**I**nfraspinatus
**t**eres minor
**S**ubscapularis

| Muscle | Notes |
|---|---|
| **S**upraspinatus | aBDucts arm before deltoid<br>Most commonly injured |
| **I**nfraspinatus | Rotates arm laterally |
| **t**eres minor | aDDucts & rotates arm laterally |
| **S**ubscapularis | aDDuct & rotates arm medially |

# ELBOW PAIN

The table below details some of the characteristic features of conditions causing elbow pain:

| Condition | Notes |
|---|---|
| **Lateral epicondylitis (tennis elbow)** | Features<br>• pain and tenderness localised to the lateral epicondyle<br>• pain worse on resisted wrist extension with the elbow extended or supination of the forearm with the elbow extended<br>• episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks |
| **Medial epicondylitis (golfer's elbow)** | Features<br>• pain and tenderness localised to the medial epicondyle<br>• pain is aggravated by wrist flexion and pronation<br>• symptoms may be accompanied by numbness / tingling in the 4th and 5th finger due to ulnar nerve involvement |
| **Radial tunnel syndrome** | Most commonly due to compression of the posterior interosseous branch of the radial nerve. It is thought to be a result of overuse.<br>Features |

| Condition | Notes |
|---|---|
| | - symptoms are similar to lateral epicondylitis making it difficult to diagnose<br>- however, the pain tends to be around 4-5 cm distal to the lateral epicondyle<br>- symptoms may be worsened by extending the elbow and pronating the forearm |
| **Cubital tunnel syndrome** | Due to the compression of the ulnar nerve.<br>Features<br>- initially intermittent tingling in the 4th and 5th finger<br>- may be worse when the elbow is resting on a firm surface or flexed for extended periods<br>- later numbness in the 4th and 5th finger with associated weakness |
| **Olecranon bursitis** | Swelling over the posterior aspect of the elbow. There may be associated pain, warmth and erythema. It typically affects middle-aged male patients. |

# LATERAL EPICONDYLITIS

Lateral epicondylitis typically follows unaccustomed activity such as house painting or playing tennis ('tennis elbow'). It is most common in people aged 45-55 years and typically affects the dominant arm.

Features
- pain and tenderness localised to the lateral epicondyle
- pain worse on wrist extension against resistance with the elbow extended or supination of the forearm with the elbow extended
- episodes typically last between 6 months and 2 years. Patients tend to have acute pain for 6-12 weeks

Management options
- advice on avoiding muscle overload
- simple analgesia
- steroid injection
- physiotherapy

# CARPAL TUNNEL SYNDROME

Carpal tunnel syndrome is caused by compression of median nerve in the carpal tunnel.

History

- pain/pins and needles in thumb, index, middle finger
- unusually the symptoms may 'ascend' proximally
- patient shakes his hand to obtain relief, classically at night

Examination
- weakness of thumb abduction (abductor pollicis brevis)
- wasting of thenar eminence (NOT hypothenar)
- Tinel's sign: tapping causes paraesthesia
- Phalen's sign: flexion of wrist causes symptoms

Causes
- idiopathic
- pregnancy
- oedema e.g. heart failure
- lunate fracture
- rheumatoid arthritis

Electrophysiology
- motor + sensory: prolongation of the action potential

Treatment
- corticosteroid injection
- wrist splints at night
- surgical decompression (flexor retinaculum division)

# CUBITAL TUNNEL SYNDROME

Cubital tunnel syndrome occurs due to compression of the ulnar nerve as it passes through the cubital tunnel.

Clincial features
- Tingling and numbness of the 4th and 5th finger which starts off intermittent and then becomes constant.
- Over time patients may also develop weakness and muscle wasting
- Pain worse on leaning on the affected elbow
- Often a history of osteoarthritis or prior trauma to the area.

Investigations
- the diagnosis is usually clinical
- however, in selected cases nerve conduction studies may be used

Management

- Avoid aggravating activity
- Physiotherapy
- Steroid injections
- Surgery in resistant cases

## DE QUERVAIN'S TENOSYNOVITIS

De Quervain's tenosynovitis is a common condition in which the sheath containing the extensor pollicis brevis and abductor pollicis longus tendons is inflamed. It typically affects females aged 30 - 50 years old.

Features
- pain on the radial side of the wrist
- tenderness over the radial styloid process
- abduction of the thumb against resistance is painful
- Finkelstein's test: the examiner pulls the thumb of the patient in ulnar deviation and longitudinal traction. In a patient with tenosynovitis this action causes pain over the radial styloid process and along the length of extensor pollisis brevis and abductor pollicis longus

Management
- analgesia
- steroid injection
- immobilisation with a thumb splint (spica) may be effective
- surgical treatment is sometimes required

## ADHESIVE CAPSULITIS

Adhesive capsulitis (frozen shoulder) is a common cause of shoulder pain. It is most common in middle-aged females. The aetiology of frozen shoulder is not fully understood.

Associations
- diabetes mellitus: up to 20% of diabetics may have an episode of frozen shoulder

Features typically develop over days
- external rotation is affected more than internal rotation or abduction
- both active and passive movement are affected
- patients typically have a painful freezing phase, an adhesive phase and a recovery phase
- bilateral in up to 20% of patients
- the episode typically lasts between 6 months and 2 years

The diagnosis is usually clinical although imaging may be required for atypical or persistent symptoms.

Management
- no single intervention has been shown to improve outcome in the long-term
- treatment options include NSAIDs, physiotherapy, oral corticosteroids and intra-articular corticosteroids

## LOWER BACK PAIN

Lower back pain (LBP) is one of the most common presentations seen in practice. Whilst the majority of presentations will be of a non-specific muscular nature it is worth keeping in mind possible causes which may need specific treatment.

Red flags for lower back pain
- age < 20 years or > 50 years
- history of previous malignancy
- night pain
- history of trauma
- systemically unwell e.g. weight loss, fever

The table below indicates some specific causes of LBP:

| **Facet joint** | **May be acute or chronic**<br>**Pain worse in the morning and on standing**<br>**On examination there may be pain over the facets. The pain is typically worse on extension of the back** |
|---|---|
| **Spinal stenosis** | Usually gradual onset<br>Unilateral or bilateral leg pain (with or without back pain), numbness, and weakness which is worse on walking. Resolves when sits down. Pain may be described as 'aching', 'crawling'.<br>Relieved by sitting down, leaning forwards and crouching down<br>Clinical examination is often normal<br>Requires MRI to confirm diagnosis |
| **Ankylosing spondylitis** | Typically a young man who presents with lower back pain and stiffness<br>Stiffness is usually worse in morning and improves with activity<br>Peripheral arthritis (25%, more common if female) |
| **Peripheral arterial disease** | Pain on walking, relieved by rest<br>Absent or weak foot pulses and other signs of limb ischaemia<br>Past history may include smoking and other vascular diseases |

## LOWER BACK PAIN: PROLAPSED DISC

A prolapsed lumbar disc usually produces clear dermatomal leg pain associated with neurological deficits.

Features
- leg pain usually worse than back
- pain often worse when sitting

The table below demonstrates the expected features according to the level of compression:

| Site of compression | Features |
|---|---|
| **L3 nerve root compression** | Sensory loss over anterior thigh<br>Weak quadriceps<br>Reduced knee reflex<br>Positive femoral stretch test |
| **L4 nerve root compression** | Sensory loss anterior aspect of knee<br>Weak quadriceps<br>Reduced knee reflex<br>Positive femoral stretch test |
| **L5 nerve root compression** | Sensory loss dorsum of foot<br>Weakness in foot and big toe dorsiflexion<br>Reflexes intact<br>Positive sciatic nerve stretch test |
| **S1 nerve root compression** | Sensory loss posterolateral aspect of leg and lateral aspect of foot<br>Weakness in plantar flexion of foot<br>Reduced ankle reflex<br>Positive sciatic nerve stretch test |

Management
- similar to that of other musculoskeletal lower back pain: analgesia, physiotherapy, exercises
- if symptoms persist 9e.g. after 4-6 weeks) then referral for consideration of MRI is appropriate

# LUMBAR SPINAL STENOSIS

Lumbar spinal stenosis is a condition in which the central canal is narrowed by tumour, disk prolapse or other similar degenerative changes.

Patients may present with a combination of back pain, neuropathic pain and symptoms mimicking claudication. One of the main features that may help to differentiate it from true claudication in the history is the positional element to the pain. Sitting is better than standing and patients may find it easier to walk uphill rather than downhill. The neurogenic claudication type history makes lumbar spinal stenosis a likely underlying diagnosis, the absence of such symptoms makes it far less likely.

**Pathology**

Degenerative disease is the commonest underlying cause. Degeneration is believed to begin in the intervertebral disk where biochemical changes such as cell death and loss of proteoglycan and water content lead to progressive disk bulging and collapse. This process leads to an increased stress transfer to the posterior facet joints, which accelerates cartilaginous degeneration, hypertrophy, and osteophyte formation; this is associated with thickening and distortion of the ligamentum flavum. The combination of the ventral disk bulging, osteophyte formation at the dorsal facet, and ligamentum flavum hyptertrophy combine to circumferentially narrow the spinal canal and the space available for the neural elements. The compression of the nerve roots of the cauda equina leads to the characteristic clinical signs and symptoms of lumbar spinal stenosis.

**Diagnosis**

MRI scanning is the best modality for demonstrating the canal narrowing. Historically a bicycle test was used as true vascular claudicants could not complete the test.

**Treatment**

Laminectomy

# SERONEGATIVE SPONDYLOARTHROPATHIES

Common features
- associated with HLA-B27
- rheumatoid factor negative - hence 'seronegative'
- peripheral arthritis, usually asymmetrical
- sacroiliitis
- enthesopathy: e.g. Achilles tendonitis, plantar fasciitis
- extra-articular manifestations: uveitis, pulmonary fibrosis (upper zone), amyloidosis, aortic regurgitation

Spondyloarthropathies
- ankylosing spondylitis
- psoriatic arthritis
- Reiter's syndrome (including reactive arthritis)
- enteropathic arthritis (associated with IBD)

# ANKYLOSING SPONDYLITIS: FEATURES

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy. It typically presents in males (sex ratio 3:1) aged 20-30 years old.

Features
- typically a young man who presents with lower back pain and stiffness of insidious onset
- stiffness is usually worse in the morning and improves with exercise
- the patient may experience pain at night which improves on getting up

Clinical examination
- reduced lateral flexion
- reduced forward flexion - Schober's test - a line is drawn 10 cm above and 5 cm below the back dimples (dimples of Venus). The distance between the two lines should increase by more than 5 cm when the patient bends as far forward as possible
- reduced chest expansion

Other features - the 'A's
- Apical fibrosis
- Anterior uveitis
- Aortic regurgitation
- Achilles tendonitis
- AV node block
- Amyloidosis

- and cauda equina syndrome
- peripheral arthritis (25%, more common if female)

## ANKYLOSING SPONDYLITIS: INVESTIGATION AND MANAGEMENT

Ankylosing spondylitis is a HLA-B27 associated spondyloarthropathy. It typically presents in males (sex ratio 3:1) aged 20-30 years old.

Investigation
Inflammatory markers (ESR, CRP) are typically raised although normal levels do not exclude ankylosing spondylitis.

HLA-B27 is of little use in making the diagnosis as it is positive in:
- 90% of patients with ankylosing spondylitis
- 10% of normal patients

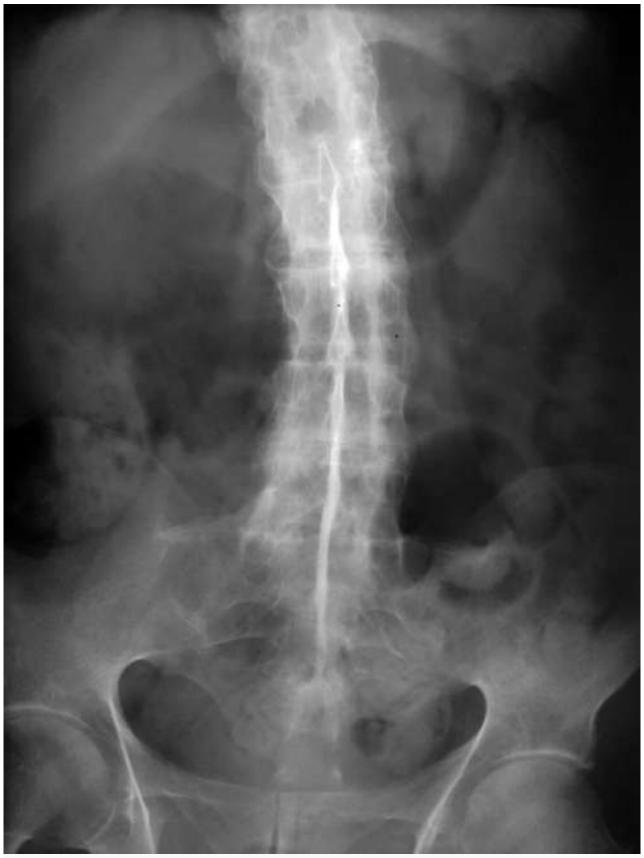
Plain x-ray of the sacroiliac joints is the most useful investigation in establishing the diagnosis. Radiographs may be normal early in disease, later changes include:
- sacroiliitis: subchondral erosions, sclerosis
- squaring of lumbar vertebrae
- 'bamboo spine' (late & uncommon)
- syndesmophytes: due to ossification of outer fibers of annulus fibrosus
- chest x-ray: apical fibrosis

If the x-ray is negative for sacroiliac joint involvement in ankylosing spondylitis but suspicion for AS remains high, the next step in the evaluation should be obtaining an MRI. Signs of early inflammation involving sacroiliac joints (bone marrow oedema) confirm the diagnosis of AS and prompt further treatment.

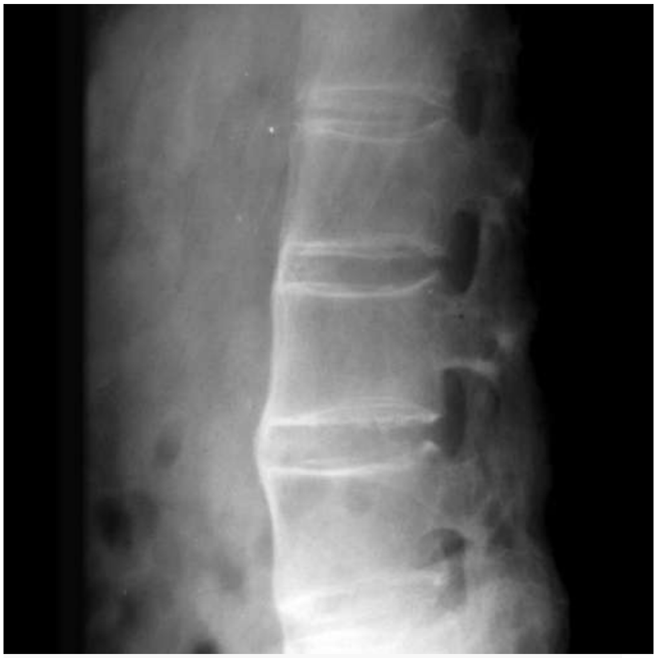
Spirometry may show a restrictive defect due to a combination of pulmonary fibrosis, kyphosis and ankylosis of the costovertebral joints.

**Management**
The following is partly based on the 2010 EULAR guidelines (please see the link for more details):
- encourage regular exercise such as swimming
- NSAIDs are the first-line treatment
- physiotherapy
- the disease-modifying drugs which are used to treat rheumatoid arthritis (such as sulphasalazine) are only really useful if there is peripheral joint involvement
- the 2010 EULAR guidelines suggest: 'Anti-TNF therapy should be given to patients with persistently high disease activity despite conventional treatments'

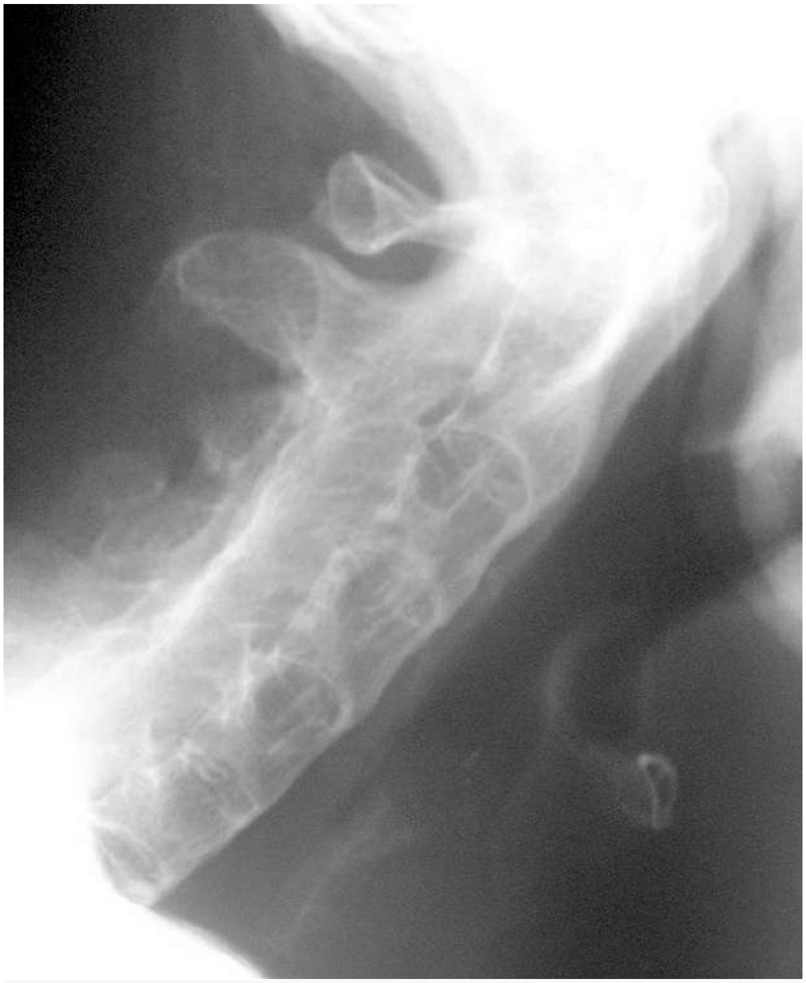
- research is ongoing to see whether anti-TNF therapies such as etanercept and adalimumab should be used earlier in the course of the disease



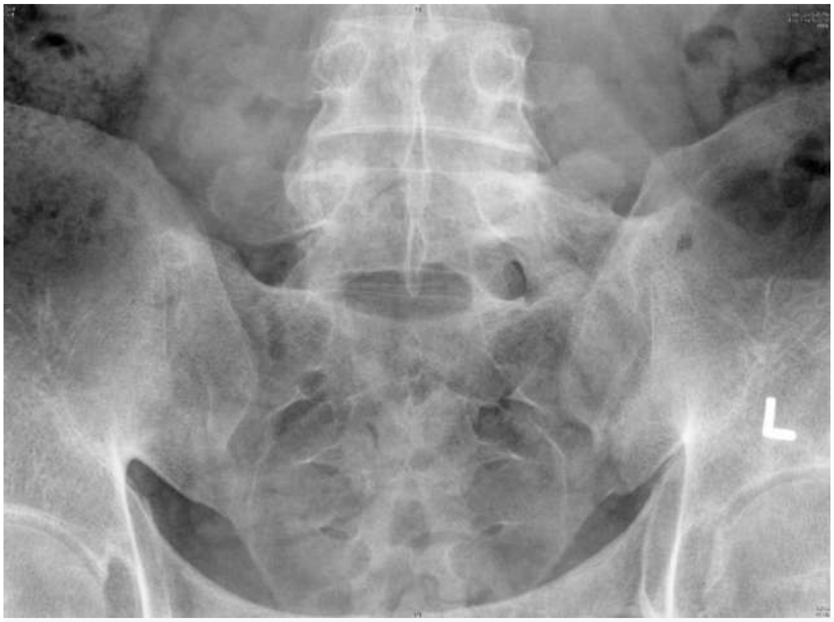
40-year-old male. There is typical appearance of bamboo spine with a single central radiodense line related to ossification of supraspinous and interspinous ligaments which is called dagger sign. Ankylosing is detectable in both sacroiliac joints



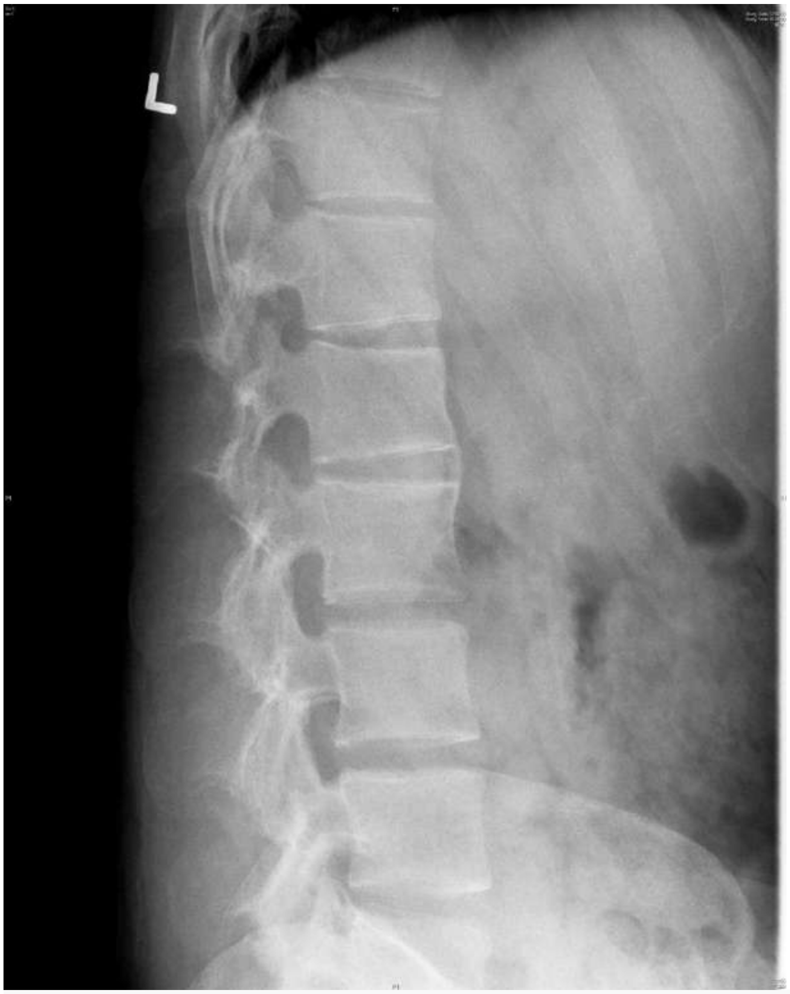
Ankylosing spondylitis with well formed syndesmophytes



Lateral cervical spine. Complete fusion of anterior and posterior elements in ankylosing spondylitis, so called bamboo spine



Fusion of bilateral sacroiliac joints. Sacroiliitis may present as sclerosis of joint margins which can be asymmetrical at early stage of disease, but is bilateral and symmetrical in late disease



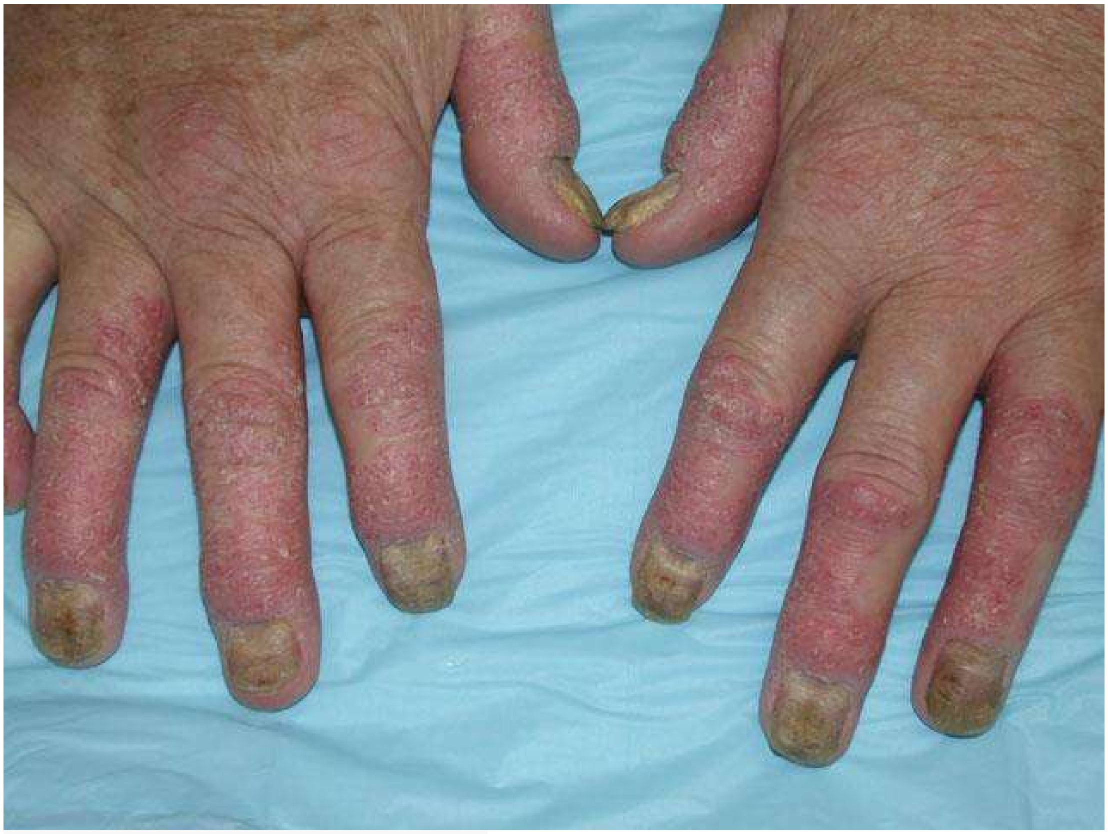
Syndesmophytes and squaring of vertebral bodies. Squaring of anterior vertebral margins is due to osteitis of anterior corners. Syndesmophytes are due to ossification of outer fibers of annulus fibrosus

# PSORIATIC ARTHROPATHY

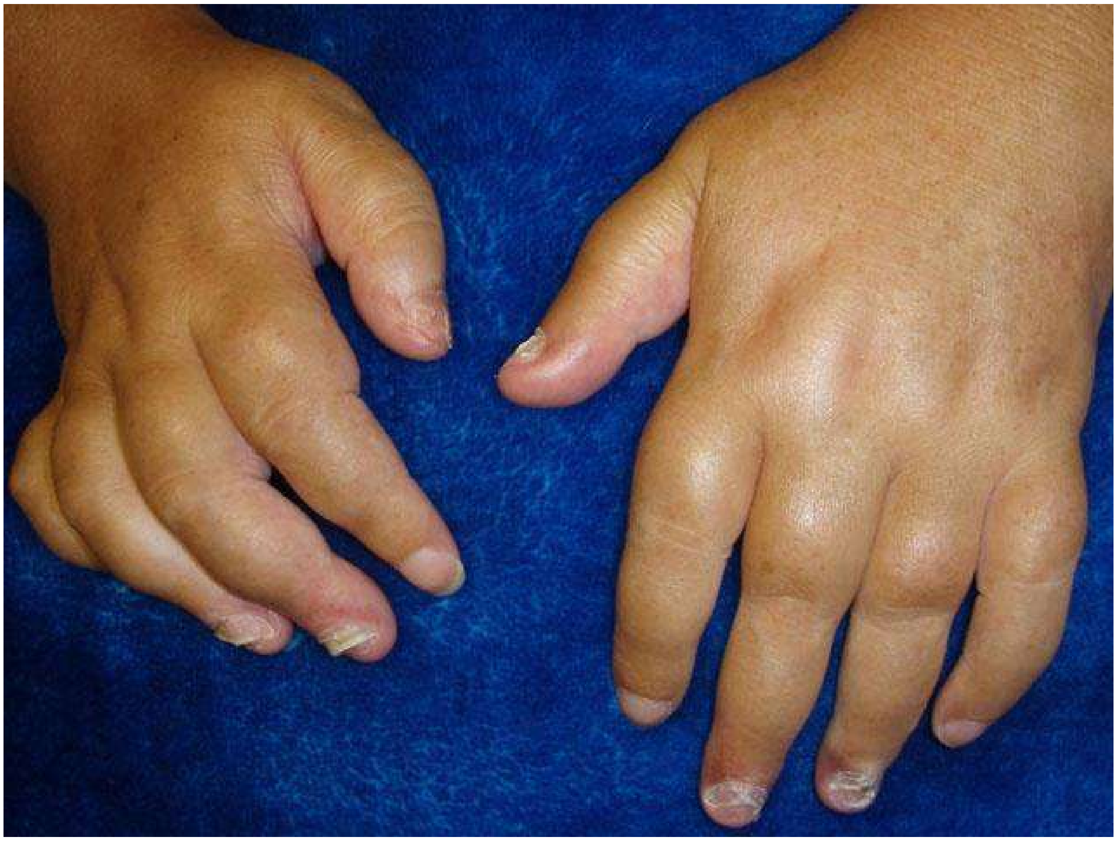
Psoriatic arthropathy correlates poorly with cutaneous psoriasis and often precedes the development of skin lesions. Around 10-20% percent of patients with skin lesions develop an arthropathy with males and females being equally affected

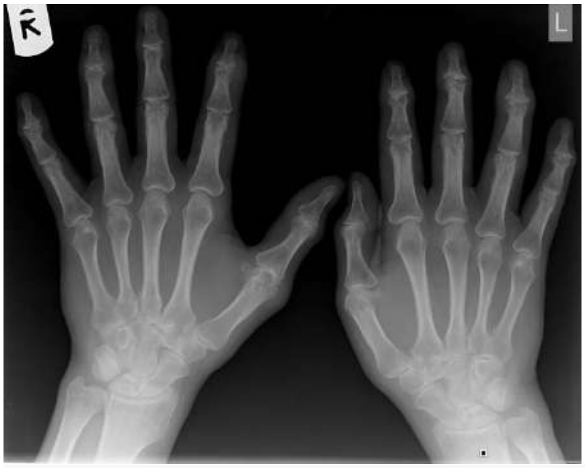
Types*
- rheumatoid-like polyarthritis: (30-40%, most common type)
- asymmetrical oligoarthritis: typically affects hands and feet (20-30%)
- sacroilitis
- DIP joint disease (10%)
- arthritis mutilans (severe deformity fingers/hand, 'telescoping fingers')

Management
- should be managed by a rheumatologist
- treat as rheumatoid arthritis but better prognosis

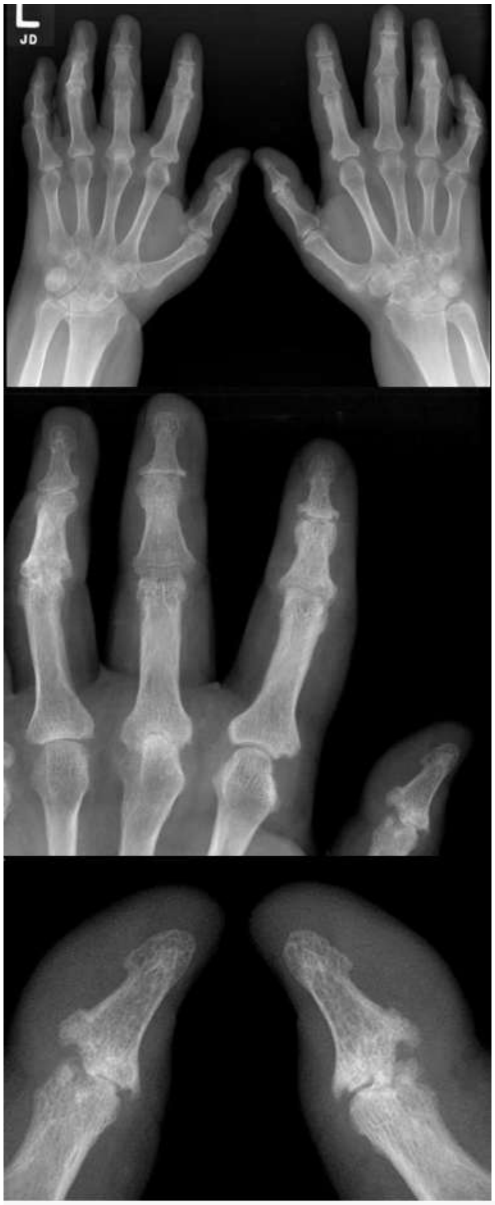


Notice the nail changes on this image as well





X-ray showing some of changes in seen in psoriatic arthropathy. Note that the DIPs are predominately affected, rather than the MCPs and PIPs as would be seen with rheumatoid. Extensive juxta-articular periostitis is seen in the DIPs but the changes have not yet progressed to the classic 'pencil-in-cup' changes that are often seen.



This x-ray shows changes affecting both the PIPs and DIPs. The close-up images show extensive changes including large eccentric erosions, tuft resorption and progresion towards a 'pencil-in-cup' changes.

*Until recently it was thought asymmetrical oligoarthritis was the most common type, based on data from the original 1973 Moll and Wright paper. Please see the link for a comparison of more recent studies

# REACTIVE ARTHRITIS

Reactive arthritis is one of the HLA-B27 associated seronegative spondyloarthropathies. It encompasses Reiter's syndrome, a term which described a classic triad of urethritis, conjunctivitis and arthritis following a dysenteric illness during the Second World War. Later studies identified patients who developed symptoms following a sexually transmitted infection (post-STI, now sometimes referred to as sexually acquired reactive arthritis, SARA).

Reactive arthritis is defined as an arthritis that develops following an infection where the organism cannot be recovered from the joint.

***'Can't see, pee or climb a tree'***

Epidemiology
- post-STI form much more common in men (e.g. 10:1)
- post-dysenteric form equal sex incidence

The table below shows the organisms that are most commonly associated with reactive arthritis:

| Post-dysenteric form | Post-STI form |
|---|---|
| *Shigella* flexneri<br>*Salmonella typhi*murium<br>*Salmonella* enteritidis<br>*Yersinia enterocolitica*<br>*Campylobacter* | *Chlamydia trachomatis* |

Management
- symptomatic: analgesia, NSAIDS, intra-articular steroids
- sulfasalazine and methotrexate are sometimes used for persistent disease
- symptoms rarely last more than 12 months

# REACTIVE ARTHRITIS: FEATURES

Reactive arthritis is one of the HLA-B27 associated seronegative spondyloarthropathies. It encompasses Reiter's syndrome, a term which described a classic triad of urethritis, conjunctivitis and arthritis following a dysenteric illness during the Second World War. Later studies identified patients who developed symptoms following a sexually transmitted infection (post-STI, now sometimes referred to as sexually acquired reactive arthritis, SARA).

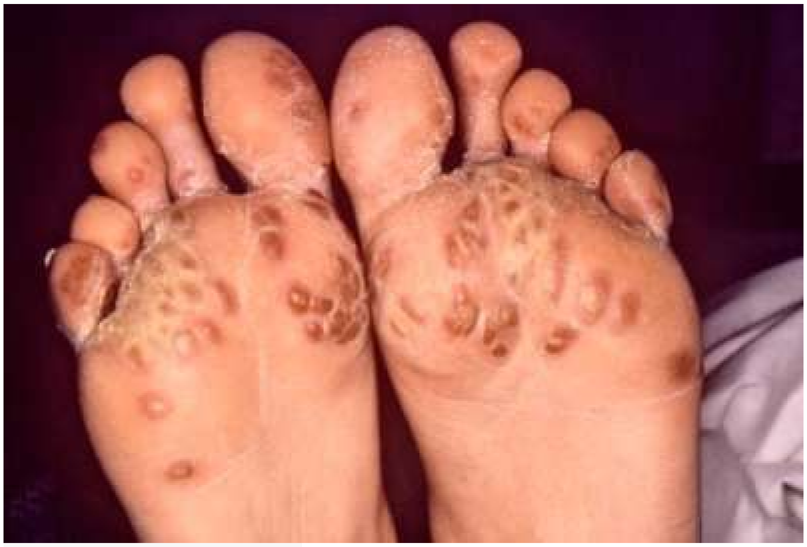
Reactive arthritis is defined as an arthritis that develops following an infection where the organism cannot be recovered from the joint.

Features

- typically develops within 4 weeks of initial infection - symptoms generally last around 4-6 months
- arthritis is typically an asymmetrical oligoarthritis of lower limbs
- dactylitis
- symptoms of urethritis
- eye: conjunctivitis (seen in 10-30%), anterior uveitis
- skin: circinate balanitis (painless vesicles on the coronal margin of the prepuce), keratoderma blenorrhagica (waxy yellow/brown papules on palms and soles)

Around 25% of patients have recurrent episodes whilst 10% of patients develop chronic disease

'Can't see, pee or climb a tree'



Keratoderma blenorrhagica

# ILIOPSOAS ABSCESS

An iliopsoas abscess describes a collection of pus in iliopsoas compartment (iliopsoas and iliacus).

Primary
- Haematogenous spread of bacteria
- Staphylococcus aureus: most common

Secondary
- Crohn's (commonest cause in this category)
- Diverticulitis, colorectal cancer
- UTI, GU cancers
- Vertebral osteomyelitis
- Femoral catheter, lithotripsy
- Endocarditis

Note the mortality rate can be up to 19-20% in secondary iliopsoas abscesses compared with 2.4% in primary abscesses.

Clinical features
- Fever
- Back/flank pain
- Limp
- Weight loss

Clinical examination
- Patient in the supine position with the knee flexed and the hip mildly externally rotated
- Specific tests to diagnose iliopsoas inflammation:
    - Place hand proximal to the patient's ipsilateral knee and ask patient to lift thigh against your hand. This will cause pain due to contraction of the psoas muscle.
    - Lie the patient on the normal side and hyperextend the affected hip. This should elicit pain as the psoas muscle is stretched.

Investigation
- CT is the gold standard

Management
- Antibiotics
- Percutaneous drainage is the initial approach and successful in around 90% of cases
- Surgery is indicated if:
    1. Failure of percutaneous drainage
    2. Presence of an another intra-abdominal pathology which requires surgery

# HIP PAIN IN ADULTS

The table below provides a brief summary of the potential causes of hip pain in adults

| Condition | Features |
|---|---|
| **Osteoarthritis** | Pain exacerbated by exercise and relieved by rest<br>Reduction in internal rotation is often the first sign<br>Age, obesity and previous joint problems are risk factors |
| **Inflammatory arthritis** | Pain in the morning<br>Systemic features<br>Raised inflammatory markers |
| **Referred lumbar spine pain** | Femoral nerve compression may cause referred pain in the hip<br>Femoral nerve stretch test may be positive - lie the patient prone. Extend the hip joint with a straight leg then bend the knee. This stretches the femoral nerve and will cause pain if it is trapped |
| **Greater trochanteric pain syndrome (Trochanteric bursitis)** | Due to repeated movement of the fibroelastic iliotibial band<br>Pain and tenderness over the lateral side of thigh<br>Most common in women aged 50-70 years |
| **Meralgia paraesthetica** | Caused by compression of lateral cutaneous nerve of thigh<br>Typically burning sensation over antero-lateral aspect of thigh |
| **Avascular necrosis** | Symptoms may be of gradual or sudden onset<br>May follow high dose steroid therapy or previous hip fracture of dislocation |
| **Pubic symphysis dysfunction** | Common in pregnancy<br>Ligament laxity increases in response to hormonal changes of pregnancy<br>Pain over the pubic symphysis with radiation to the groins and the medial aspects of the thighs. A waddling gait may be seen |
| **Transient idiopathic osteoporosis** | An uncommon condition sometimes seen in the third trimester of pregnancy<br>Groin pain associated with a limited range of movement in the hip<br>Patients may be unable to weight bear<br>ESR may be elevated |

# AVASCULAR NECROSIS OF THE HIP

Avascular necrosis (AVN) may be defined as death of bone tissue secondary to loss of the blood supply. This leads to bone destruction and loss of joint function. It most commonly affects the epiphysis of long bones such as the femur.

Causes

- long-term steroid use
- chemotherapy
- alcohol excess
- trauma

Features

- initially asymptomatic
- pain in the affected joint

Investigation

- plain x-ray findings may be normal initially. Osteopenia and microfractures may be seen early on. Collapse of the articular surface may result in the crescent sign
- MRI is the investigation of choice. It is more sensitive than radionuclide bone scanning

Management

- joint replacement may be necessary

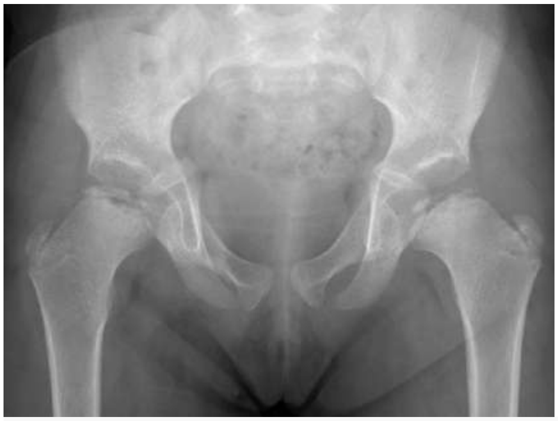
# HIP PROBLEMS IN CHILDREN

The table below provides a brief summary of the potential causes of hip problems in children

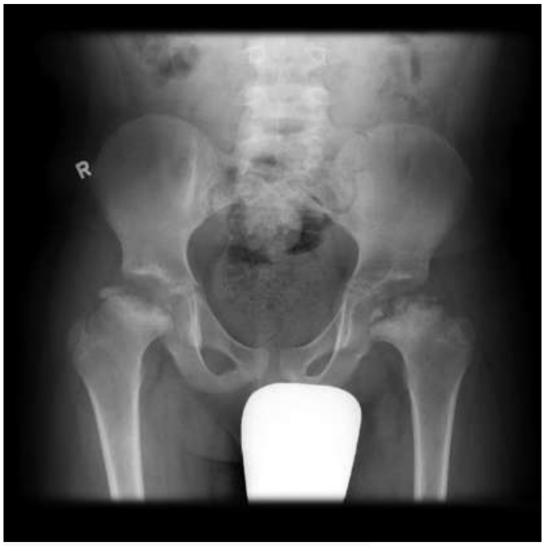
| Condition | Notes |
|---|---|
| **Development dysplasia of the hip** | Often picked up on newborn examination<br>Barlow's test, Ortolani's test are positive<br>Unequal skin folds/leg length |
| **Transient synovitis (irritable hip)** | Typical age group = 2-10 years<br>Acute hip pain associated with viral infection<br>Commonest cause of hip pain in children |
| **Perthes disease** | Perthes disease is a degenerative condition affecting the hip joints of children, typically between the ages of 4-8 years. It is due to avascular necrosis of the femoral head<br>Perthes disease is 5 times more common in boys. Around 10% of cases are bilateral<br>Features<br>• hip pain: develops progressively over a few weeks<br>• limp<br>• stiffness and reduced range of hip movement<br>• x-ray: early changes include widening of joint space, later changes include decreased femoral head size/flattening |
| **Slipped upper femoral epiphysis** | Typical age group = 10-15 years<br>More common in obese children and boys<br>Displacement of the femoral head epiphysis postero-inferiorly<br>Bilateral slip in 20% of cases<br>May present acutely following trauma or more commonly with chronic, persistent symptoms<br>Features<br>• knee or distal thigh pain is common<br>• loss of internal rotation of the leg in flexion |
| **Juvenile idiopathic arthritis (JIA)** | Preferred to the older term juvenile chronic arthritis, describes arthritis occurring in someone who is less than 16 years old that lasts for more than three months.<br>Pauciarticular JIA refers to cases where 4 or less joints are affected. It accounts for around 60% of cases of JIA<br>Features of pauciarticular JIA |

| Condition | Notes |
|---|---|
| | - joint pain and swelling: usually medium sized joints e.g. knees, ankles, elbows<br>- limp<br>- ANA may be positive in JIA - associated with anterior uveitis |
| **Septic arthritis** | Acute hip pain associated with systemic upset e.g. pyrexia. Inability/severe limitation of affected joint |

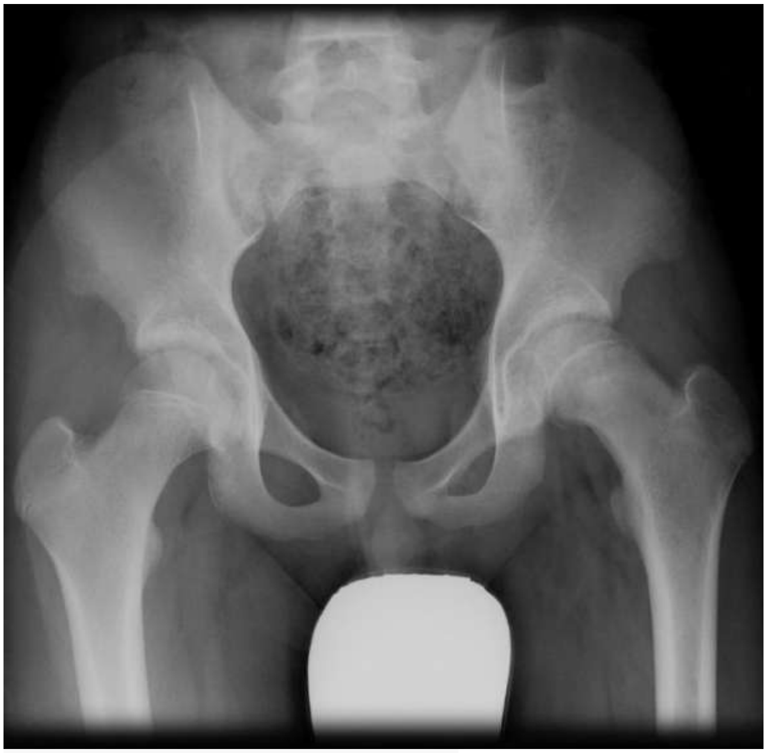
## Image gallery



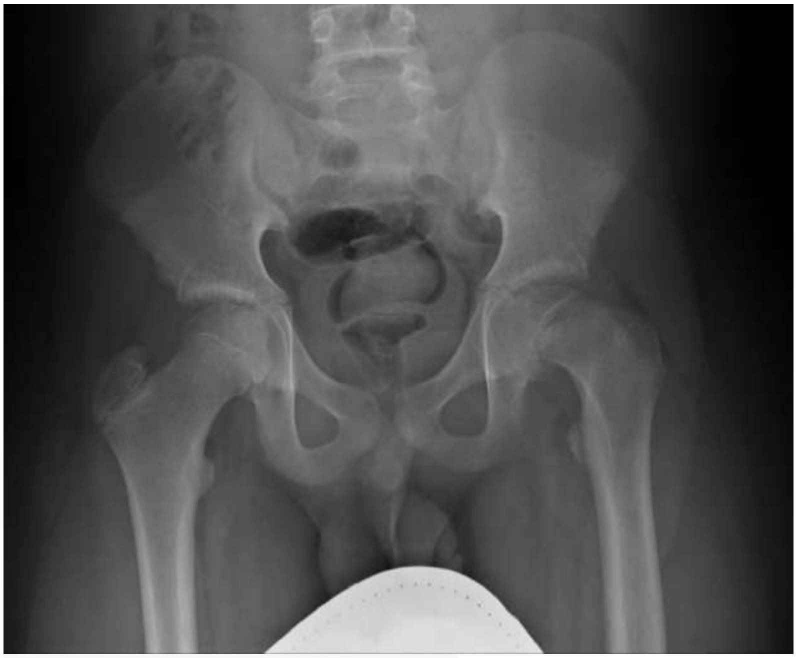
Perthes disease - both femoral epiphyses show extensive destruction, the acetabula are deformed



Perthes disease - bilateral disease



Slipped upper femoral epiphysis - left side



Slipped upper femoral epiphysis - left side

# SEPTIC ARTHRITIS

Overview
- most common organism overall is Staphylococcus aureus
- in young adults who are sexually active Neisseria gonorrhoeae should also be considered
- in adults, the most common location is the knee

The Kocher criteria for the diagnosis of septic arthritis:
- fever >38.5 degrees C
- non-weight bearing
- raised ESR
- raised WCC

Management
- synovial fluid should be obtained before starting treatment
- intravenous antibiotics which cover Gram-positive cocci are indicated. The BNF currently recommends flucloxacillin or clindamycin if penicillin allergic
- antibiotic treatment is normally be given for several weeks (BNF states 6-12 weeks)
- needle aspiration should be used to decompress the joint
- arthroscopic lavage may be required

# MERALGIA PARAESTHETICA

Meralgia paraesthetica comes from the Greek words meros for thigh and algos for pain and is often described as a syndrome of paraesthesia or anaesthesia in the distribution of the lateral femoral cutaneous nerve (LFCN). It is an entrapment mononeuropathy of the LFCN, but can also be iatrogenic after a surgical procedure, or result from a neuroma. Although uncommon, meralgia paraesthetica is not rare and is hence probably underdiagnosed.

Anatomy
- The LFCN is primarily a sensory nerve, carrying no motor fibres.
- It most commonly originates from the L2/3 segments.
- After passing behind the psoas muscle, it runs beneath the iliac fascia as it crosses the surface of the iliac muscle and eventually exits through or under the lateral aspect of the inguinal ligament.
- As the nerve curves medially and inferiorly around the anterior superior iliac spine (ASIS), it may be subject to repetitive trauma or pressure.
- Compression of this nerve anywhere along its course can lead to the development of meralgia paraesthetica.

Epidemiology
- The majority of cases occur in people aged between 30 and 40.

- In some, both legs may be affected.
- It is more common in men than women.
- Occurs more commonly in those with diabetes than in the general population.

Risk factors 3
- Obesity
- Pregnancy
- Tense ascites
- Trauma
- Iatrogenic, such as pelvic osteotomy, spinal surgeries, laparoscopic hernia repair and bariatric surgery. In some cases, may result from abduction splints used in the management of Perthe's disease.
- Various sports have been implicated, including gymnastics, football, bodybuilding and strenuous exercise.
- Some cases are idiopathic.

Patients typically present with the following symptoms in the upper lateral aspect of the thigh:
- Burning, tingling, coldness, or shooting pain
- Numbness
- Deep muscle ache
- Symptoms are usually aggravated by standing, and relieved by sitting
- They can be mild and resolve spontaneously or may severely restrict the patient for many years.

Signs:
- Symptoms may be reproduced by deep palpation just below the ASIS (pelvic compression) and also by extension of the hip.
- There is altered sensation over the upper lateral aspect of the thigh.
- There is no motor weakness.

Investigations:
- The pelvic compression test is highly sensitive, and often, meralgia paraesthetica can be diagnosed based on this test alone
- Injection of the nerve with local anaesthetic will abolish the pain. Using ultrasound is effective both for diagnosis and guiding injection therapy in meralgia paraesthetica
- Nerve conduction studies may be useful.

## ANKLE INJURY: OTTAWA RULES

The Ottawa Rules with for ankle x-rays have a sensitivity approaching 100%

An ankle x-ray is required only if there is any pain in the malleolar zone and any one of the following findings:

- bony tenderness at the lateral malleolar zone (from the tip of the lateral malleolus to include the lower 6 cm of posterior border of the fibular)
- bony tenderness at the medial malleolar zone (from the tip of the medial malleolus to the lower 6 cm of the posterior border of the tibia)
- inability to walk four weight bearing steps immediately after the injury and in the emergency department

There are also Ottawa rules available for both foot and knee injuries

# OSTEOARTHRITIS: MANAGEMENT

NICE published guidelines on the management of osteoarthritis (OA) in 2014

- all patients should be offered help with weight loss, given advice about local muscle strengthening exercises and general aerobic fitness
- paracetamol and topical NSAIDs are first-line analgesics. Topical NSAIDs are indicated only for OA of the knee or hand
- second-line treatment is oral NSAIDs/COX-2 inhibitors, opioids, capsaicin cream and intra-articular corticosteroids. A proton pump inhibitor should be co-prescribed with NSAIDs and COX-2 inhibitors. These drugs should be avoided if the patient takes aspirin
- non-pharmacological treatment options include supports and braces, TENS and shock absorbing insoles or shoes
- if conservative methods fail then refer for consideration of joint replacement

What is the role of glucosamine?

- normal constituent of glycosaminoglycans in cartilage and synovial fluid
- a systematic review of several double blind RCTs of glucosamine in knee osteoarthritis reported significant short-term symptomatic benefits including significantly reduced joint space narrowing and improved pain scores
- more recent studies have however been mixed
- the 2008 NICE guidelines suggest it is not recommended
- a 2008 Drug and Therapeutics Bulletin review advised that whilst glucosamine provides modest pain relief in knee osteoarthritis it should not be prescribed on the NHS due to limited evidence of cost-effectiveness

# OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta (more commonly known as brittle bone disease) is a group of disorders of collagen metabolism resulting in bone fragility and fractures. The most common, and milder, form of osteogenesis imperfecta is type 1

Overview

- autosomal dominant
- abnormality in type 1 collagen due to decreased synthesis of pro-alpha 1 or pro-alpha 2 collagen polypeptides

Features

- presents in childhood
- fractures following minor trauma
- blue sclera
- deafness secondary to otosclerosis
- dental imperfections are common

Investigations
- adjusted calcium, phosphate, parathyroid hormone and ALP results are usually normal in osteogenesis imperfecta

# OSTEOMALACIA

Basics
- normal bony tissue but decreased mineral content
- rickets if when growing
- osteomalacia if after epiphysis fusion

Types
- vitamin D deficiency e.g. malabsorption, lack of sunlight, diet
- renal failure
- drug induced e.g. anticonvulsants
- vitamin D resistant; inherited
- liver disease, e.g. cirrhosis

Features
- rickets: knock-knee, bow leg, features of hypocalcaemia
- osteomalacia: bone pain, fractures, muscle tenderness, proximal myopathy

Investigation
- low 25(OH) vitamin D (in 100% of patients, by definition)
- raised alkaline phosphatase (in 95-100% of patients)
- low calcium, phosphate (in around 30%)
- x-ray: children - cupped, ragged metaphyseal surfaces; adults - translucent bands (Looser's zones or pseudofractures)

Treatment
- calcium with vitamin D tablets

# OSTEOMYELITIS

Osteomyelitis describes an infection of the bone.

Staph. aureus is the most common cause except in patients with sickle-cell anaemia where Salmonella species predominate.

Predisposing conditions

- diabetes mellitus
- sickle cell anaemia
- intravenous drug user
- immunosuppression due to either medication or HIV
- alcohol excess

Investigations

- MRI is the imaging modality of choice, with a sensitivity of 90-100%

Management

- flucloxacillin for 6 weeks
- clindamycin if penicillin-allergic

# OSTEOPETROSIS

Overview

- also known as marble bone disease
- rare disorder of defective osteoclast function resulting in failure of normal bone resorption
- results in dense, thick bones that are prone to fracture
- bone pains and neuropathies are common.
- calcium, phosphate and ALP are normal
- stem cell transplant and interferon-gamma have been used for treatment

# OSTEOPOROSIS: CAUSES

Advancing age and female sex are significant risk factors for osteoporosis. Prevalence of osteoporosis increases from 2% at 50 years to more than 25% at 80 years in women.

There are many other risk factors and secondary causes of osteoporosis. We'll start by looking at the most 'important' ones - these are risk factors that are used by major risk assessment tools such as FRAX:

- history of glucocorticoid use
- rheumatoid arthritis
- alcohol excess
- history of parental hip fracture
- low body mass index
- current smoking

Other risk factors

- sedentary lifestyle
- premature menopause
- Caucasians and Asians
- endocrine disorders: hyperthyroidism, hypogonadism (e.g. Turner's, testosterone deficiency), growth hormone deficiency, hyperparathyroidism, diabetes mellitus
- multiple myeloma, lymphoma
- gastrointestinal disorders: inflammatory bowel disease, malabsorption (e.g. Coeliac's), gastrectomy, liver disease
- chronic kidney disease
- osteogenesis imperfecta, homocystinuria

Medications that may worsen osteoporosis (other than glucocorticoids):

- SSRIs
- antiepileptics
- proton pump inhibitors
- glitazones
- long term heparin therapy
- aromatase inhibitors e.g. anastrozole

**Investigations for secondary causes**

If a patient is diagnosed with osteoporosis or has a fragility fracture further investigations may be warranted. NOGG recommend testing for the following reasons:

- exclude diseases that mimic osteoporosis (e.g. osteomalacia, myeloma);
- identify the cause of osteoporosis and contributory factors;
- assess the risk of subsequent fractures;
- select the most appropriate form of treatment

The following investigations are recommended by NOGG:

- History and physical examination
- Blood cell count, sedimentation rate or C-reactive protein, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase and liver transaminases
- Thyroid function tests
- Bone densitometry ( DXA)

Other procedures, if indicated

- Lateral radiographs of lumbar and thoracic spine/DXA-based vertebral imaging
- Protein immunoelectrophoresis and urinary Bence-Jones proteins
- 25OHD
- PTH
- Serum testosterone, SHBG, FSH, LH (in men),
- Serum prolactin
- 24 hour urinary cortisol/dexamethasone suppression test
- Endomysial and/or tissue transglutaminase antibodies (coeliac disease)
- Isotope bone scan
- Markers of bone turnover, when available
- Urinary calcium excretion

So from the first list we should order the following bloods as a minimum for all patients:

- full blood count
- urea and electrolytes
- liver function tests
- bone profile
- CRP
- thyroid function tests

# OSTEOPOROSIS: GLUCOCORTICOID-INDUCED

We know that one of the most important risk factors for osteoporosis is the use of corticosteroids. As these drugs are so widely used in clinical practice it is important we manage this risk appropriately.

The most widely followed guidelines are based around the 2002 Royal College of Physicians (RCP) 'Glucocorticoid-induced osteoporosis: A concise guide to prevention and treatment'.

The risk of osteoporosis is thought to rise significantly once a patient is taking the equivalent of prednisolone 7.5mg a day for 3 or more months. It is important to note that we should manage patients in an anticipatory, i.e. if it likely that the patient will have to take steroids for at least 3 months then we should start bone protection straight away, rather than waiting until 3 months has elapsed. A good example is a patient with newly diagnosed polymyalgia rheumatica. As it is very likely they will be on a significant dose of prednisolone for greater than 3 months bone protection should be commenced immediately.

**Management of patients at risk of corticosteroid-induced osteoporosis**
The RCP guidelines essentially divide patients into two groups.

1. Patients over the age of 65 years or those who've previously had a fragility fracture should be offered bone protection.

2. Patients under the age of 65 years should be offered a bone density scan, with further management dependent:

| T score | Management |
|---|---|
| Greater than 0 | Reassure |
| Between 0 and -1.5 | Repeat bone density scan in 1-3 years |
| Less than -1.5 | Offer bone protection |

The first-line treatment is alendronate. Patients should also be calcium and vitamin D replete.

# OSTEOPOROSIS: DEXA SCAN

Basics

- T score: based on bone mass of young reference population
- T score of -1.0 means bone mass of one standard deviation below that of young reference population
- Z score is adjusted for age, gender and ethnic factors

T score

- > -1.0 = normal
- -1.0 to -2.5 = osteopaenia
- < -2.5 = osteoporosis

# OSTEOPOROSIS: MANAGEMENT

NICE guidelines were updated in 2008 on the secondary prevention of osteoporotic fractures in postmenopausal women.

Key points include

- treatment is indicated following osteoporotic fragility fractures in postmenopausal women who are confirmed to have osteoporosis (a T-score of - 2.5 SD or below). In women aged 75 years or

older, a DEXA scan may not be required 'if the responsible clinician considers it to be clinically inappropriate or unfeasible'
- vitamin D and calcium supplementation should be offered to all women unless the clinician is confident they have adequate calcium intake and are vitamin D replete
- alendronate is first-line
- around 25% of patients cannot tolerate alendronate, usually due to upper gastrointestinal problems. These patients should be offered risedronate or etidronate (see treatment criteria below)
- strontium ranelate and raloxifene are recommended if patients cannot tolerate bisphosphonates (see treatment criteria below)

**Treatment criteria for patients not taking alendronate**
Unfortunately, a number of complicated treatment cut-off tables have been produced in the latest guidelines for patients who do not tolerate alendronate

These take into account a patients age, theire T-score and the number of risk factors they have from the following list:
- parental history of hip fracture
- alcohol intake of 4 or more units per day
- rheumatoid arthritis

It is very unlikely that examiners would expect you to have memorised these risk tables so we've not included them in the revision notes but they may be found by following the NICE link. The most important thing to remember is:
- the T-score criteria for risedronate or etidronate are less than the others implying that these are the second line drugs
- if alendronate, risedronate or etidronate cannot be taken then strontium ranelate or raloxifene may be given based on quite strict T-scores (e.g. a 60-year-old woman would need a T-score < -3.5)
- the strictest criteria are for denosumab

**Supplementary notes on treatment**
Bisphosphonates
- alendronate, risedronate and etidronate are all licensed for the prevention and treatment of post-menopausal and glucocorticoid-induced osteoporosis
- all three have been shown to reduce the risk of both vertebral and non-vertebral fractures although alendronate, risedronate may be superior to etidronate in preventing hip fractures
- ibandronate is a once-monthly oral bisphosphonate

Vitamin D and calcium
- poor evidence base to suggest reduced fracture rates in the general population at risk of osteoporotic fractures - may reduce rates in frail, housebound patients

Raloxifene - selective oestrogen receptor modulator (SERM)

- has been shown to prevent bone loss and to reduce the risk of vertebral fractures, but has not yet been shown to reduce the risk of non-vertebral fractures
- has been shown to increase bone density in the spine and proximal femur
- may worsen menopausal symptoms
- increased risk of thromboembolic events
- may decrease risk of breast cancer

Strontium ranelate

- 'dual action bone agent' - increases deposition of new bone by osteoblasts (promotes differentiation of pre-osteoblast to osteoblast) and reduces the resorption of bone by inhibiting osteoclasts
- concerns regarding the safety profile of strontium have been raised recently. It should only be prescribed by a specialist in secondary care
- due to these concerns the European Medicines Agency in 2014 said it should only be used by people for whom there are no other treatments for osteoporosis
- increased risk of cardiovascular events: any history of cardiovascular disease or significant risk of cardiovascular disease is a contraindication
- increased risk of thromboembolic events: a Drug Safety Update in 2012 recommended it is not used in patients with a history of venous thromboembolism
- may cause serious skin reactions such as Stevens Johnson syndrome

Denosumab

- human monoclonal antibody that inhibits RANK ligand, which in turn inhibits the maturation of osteoclasts
- given as a single subcutaneous injection every 6 months
- initial trial data suggests that it is effective and well tolerated

Teriparatide

- recombinant form of parathyroid hormone
- very effective at increasing bone mineral density but role in the management of osteoporosis yet to be clearly defined

Hormone replacement therapy

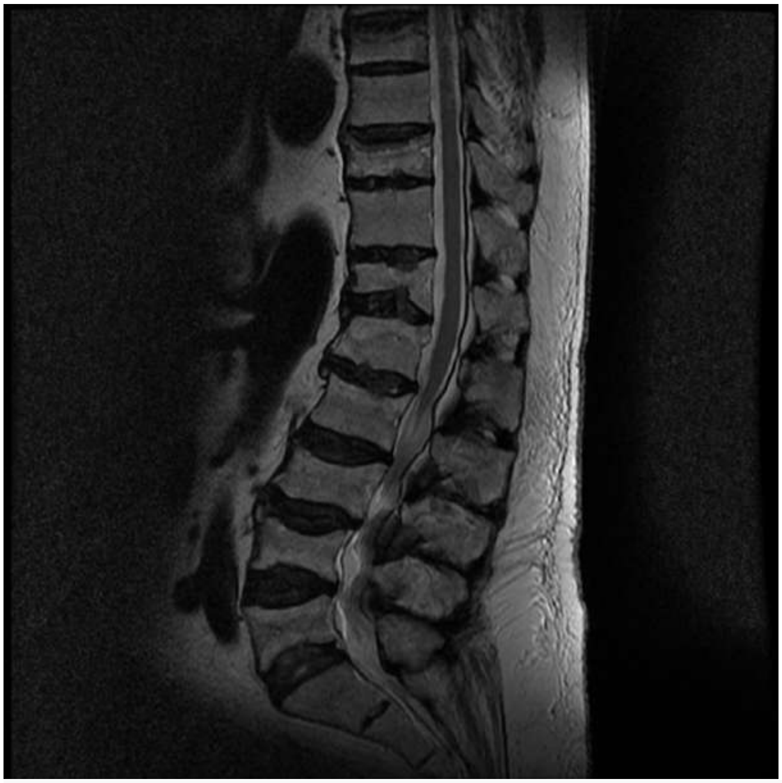
- has been shown to reduce the incidence of vertebral fracture and non-vertebral fractures
- due to concerns about increased rates of cardiovascular disease and breast cancer it is no longer recommended for primary or secondary prevention of osteoporosis unless the woman is suffering from vasomotor symptoms

Hip protectors

- evidence to suggest significantly reduce hip fractures in nursing home patients
- compliance is a problem

Falls risk assessment

- no evidence to suggest reduced fracture rates
- however, do reduce rate of falls and should be considered in management of high risk patients



MRI showing osteoporotic fractures of the 8th and 10th thoracic vertebrae.

## BISPHOSPHONATES

Bisphosphonates are analogues of pyrophosphate, a molecule which decreases demineralisation in bone. They inhibit osteoclasts by reducing recruitment and promoting apoptosis.

Clinical uses

- prevention and treatment of osteoporosis
- hypercalcaemia
- Paget's disease
- pain from bone metatases

Adverse effects

- oesophageal reactions: oesophagitis, oesophageal ulcers (especially alendronate)
- osteonecrosis of the jaw
- increased risk of atypical stress fractures of the proximal femoral shaft in patients taking alendronate
- acute phase response: fever, myalgia and arthralgia may occur following administration
- hypocalcaemia: due to reduced calcium efflux from bone. Usually clinically unimportant

The BNF suggests the following counselling for patients taking oral bisphosphonates
'Tablets should be swallowed whole with plenty of water while sitting or standing; to be given on an empty stomach at least 30 minutes before breakfast (or another oral medication); patient should stand or sit upright for at least 30 minutes after taking tablet'

Hypocalcemia/vitamin D deficiency should be corrected before giving bisphosphonates. However, when starting bisphosphonate treatment for osteoporosis, calcium should only be prescribed if dietary intake is inadequate. Vitamin D supplements are normally given.

The duration of bisphosphonate treatment varies according to the level of risk. Some authorities recommend stopping bisphosphonates at 5 years if the following apply:

- patient is < 75-years-old
- femoral neck T-score of > -2.5
- low risk according to FRAX/NOGG

# DENOSUMAB

Denosumab is a relatively new treatment for osteoporosis. It is a human monoclonal antibody that prevents the development of osteoclasts by inhibiting RANKL. Remember that osteoblasts build bone, osteoclasts eat bone. It is given as a subcutaneous injection, at a dose of 60mg, every 6 months.

A larger dose of denosumab (120mg) may also be given every 4 weeks for the prevention of skeletal-related events (i.e. pathological fractures) in adults with bone metastases from solid tumours. For example, you may have noticed some of your breast cancer patients have been prescribed denosumab.

**Where does it fit in the management of osteoporosis?**
Oral bisphosphonates are still given first-line, with oral alendronate being the first-line treatment. If alendronate is not tolerated then NICE recommend using an alternative bisphosphonate - either risedronate or etidronate. Following this the advice becomes more complicated with the next-line medications only being started if certain T score and other risk factor criteria being met. Raloxifene and strontium ranelate were recommended as next-line drugs in the NICE criteria but following recent safety concerns regarding strontium ranelate it is likely there will be an increasing role for denosumab.

NICE published a technology appraisal looking at the role of denosumab in 2010. A link is provided.

**What are the known side-effects of denosumab?**
Denosumab is generally well tolerated. Dyspnoea and diarrhoea are generally considered the two most common side effects, occurring in around 1 in 10 patients. Other less common side effects include hypocalcemia and upper respiratory tract infections.

**What does the Drug Safety Update add?**
Cases of atypical femoral fractures have been noted in patients taking denosumab. Doctors are advised to look out for patients complaining of unusual thigh, hip or groin pain.

# VITAMIN D SUPPLEMENTATION

Vitamin D supplementation has been a hot topic for a number of years now. The muddied waters are now slightly clearer following the release of the following:

- 2012: letter by the Chief Medical Officer regarding vitamin D supplementation
- 2013: National Osteoporosis Society (NOS) release UK Vitamin D guideline

The following groups should be advised to take vitamin D supplementation:

- all pregnant and breastfeeding women should take a daily supplement containing 10µg of vitamin D
- all children aged 6 months - 5 years. Babies fed with formula milk do not need to take a supplement if they are taking more than 500ml of milk a day, as formula milk is fortified with vitamin D
- adults > 65 years
- 'people who are not exposed to much sun should also take a daily supplement' e.g. housebound patients

**Testing for vitamin D deficiency**
The key message is that not many people warrant a vitamin D test. The NOS guidelines specify that testing may be appropriate in the following situations:

- patients with bone diseases that may be improved with vitamin D treatment e.g. known osteomalacia or Paget's disease
- patients with bone diseases, prior to specific treatment where correcting vitamin deficiency is appropriate e,g, prior to intravenous zolendronate or denosumab
- patients with musculoskeletal symptoms that could be attributed to vitamin D deficiency e.g. bone pain ?osteomalacia

Patients with osteoporosis should always be given calcium/vitamin D supplements so testing is not considered necessary. People who are at higher risk of vitamin D deficiency (see above) should be treated anyway so again testing is not necessary.

# PAGET'S DISEASE OF THE BONE

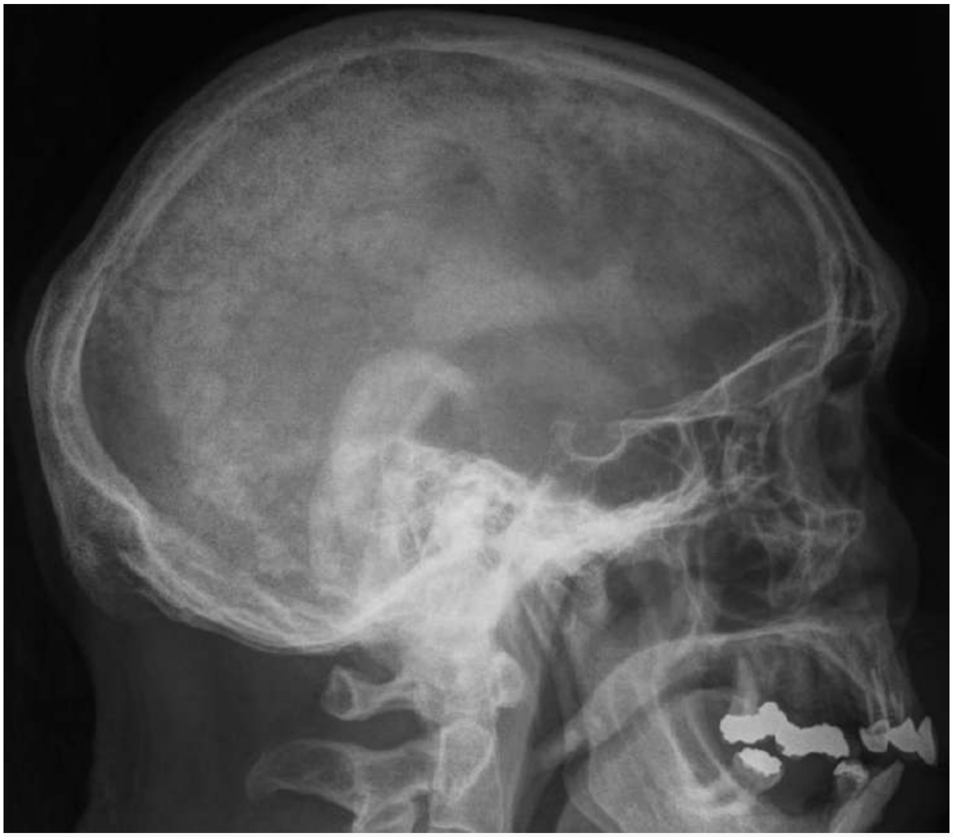
Paget's disease is a disease of increased but uncontrolled bone turnover. It is thought to be primarily a disorder of osteoclasts, with excessive osteoclastic resorption followed by increased osteoblastic activity. Paget's disease is common (UK prevalence 5%) but symptomatic in only 1 in 20 patients. The skull, spine/pelvis, and long bones of the lower extremities are most commonly affected.

Predisposing factors
- increasing age
- male sex
- northern latitude
- family history

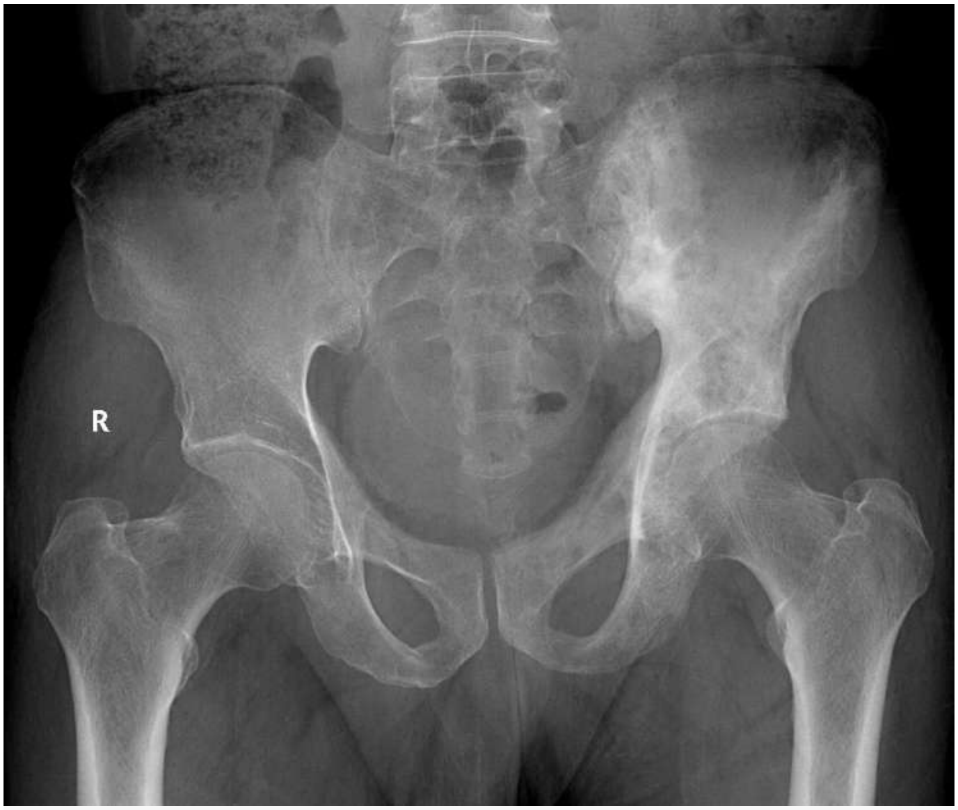
Clinical features - only 5% of patients are symptomatic
- the stereotypical presentation is an older male with bone pain and an isolated raised ALP
- bone pain (e.g. pelvis, lumbar spine, femur)
- classical, untreated features: bowing of tibia, bossing of skull
- raised alkaline phosphatase (ALP) - calcium* and phosphate are typically normal
- other markers of bone turnover include: procollagen type I N-terminal propeptide (PINP), serum C-telopeptide (CTx), urinary N-telopeptide (NTx), and urinary hydroxyproline
- skull x-ray: thickened vault, osteoporosis circumscripta

- Indications for treatment include bone pain, skull or long bone deformity, fracture, periarticular Paget's
- bisphosphonate (either oral risedronate or IV zoledronate)
- calcitonin is less commonly used now

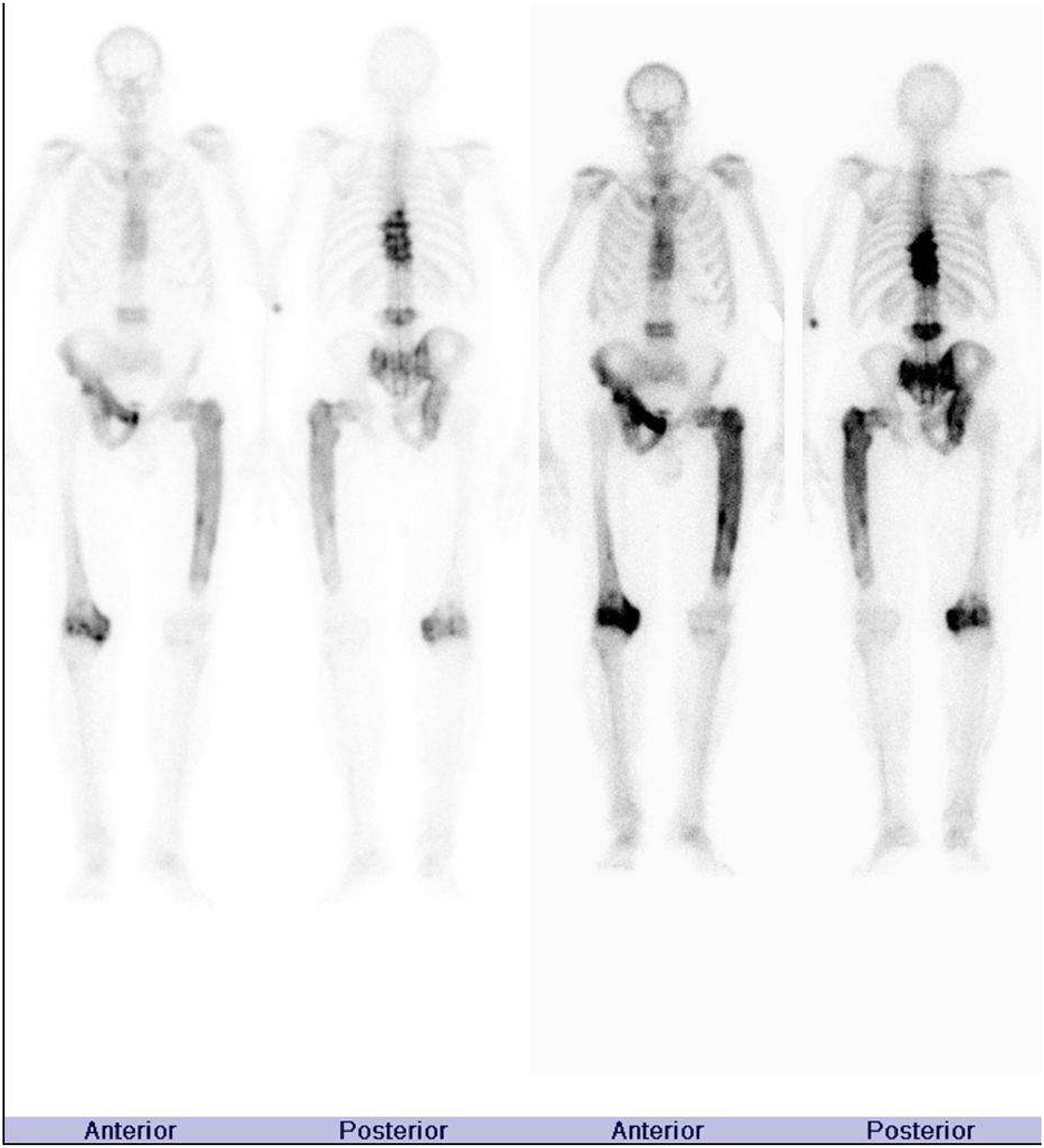
Complications
- deafness (cranial nerve entrapment)
- bone sarcoma (1% if affected for > 10 years)
- fractures
- skull thickening
- high-output cardiac failure



The radiograph demonstrates marked thickening of the calvarium. There are also ill-defined sclerotic and lucent areas throughout. These features are consistent with Paget's disease.



Pelvic x-ray from an elderly man with Paget's disease. There is a smooth cortical expansion of the left hemipelvic bones with diffuse increased bone density and coarsening of trabeculae.


Anterior
Posterior
Anterior
Posterior

Isotope bone scan from a patient with Paget's disease showing a typical distribution in the spine, asymmetrical pelvic disease and proximal long bones.

*usually normal in this condition but hypercalcaemia may occur with prolonged immobilisation

# BONE TUMOURS

## Benign tumours

| Tumour | Notes |
|---|---|
| Osteoma | - benign 'overgrowth' of bone, most typically occuring on the skull<br>- associated with Gardner's syndrome (a variant of familial adenomatous polyposis, FAP) |
| Osteochondroma (exotosis) | - most common benign bone tumour<br>- more in males, usually diagnosed in patients aged < 20 years<br>- cartilage-capped bony projection on the external surface of a bone |
| Giant cell tumour | - tumour of multinucleated giant cells within a fibrous stroma<br>- peak incidence: 20-40 years<br>- occurs most frequently in the epiphyses of long bones<br>- X-ray shows a 'double bubble' or 'soap bubble' appearance |

## Malignant tumours

| Tumour | Notes |
|---|---|
| Osteosarcoma | - most common primary malignant bone tumour<br>- seen mainly in children and adolescents<br>- occurs most frequently in the metaphyseal region of long bones prior to epiphyseal closure, with 40% occuring in the femur, 20% in the tibia, and 10% in the humerus<br>- x-ray shows Codman triangle (from periosteal elevation) and 'sunburst' pattern<br>- mutation of the Rb gene significantly increases risk of osteosarcoma (hence association with retinoblastoma)<br>- other predisposing factors include Paget's disease of the bone and radiotherapy |
| Ewing's sarcoma | - small round blue cell tumour<br>- seen mainly in children and adolescents<br>- occurs most frequently in the pelvis and long bones. Tends to cause severe pain<br>- associated with t(11;22) translocation which results in an EWS-FLI1 gene product<br>- x-ray shows 'onion skin' appearance |
| Chondrosarcoma | - malignant tumour of cartilage<br>- most commonly affects the axial skeleton<br>- more common in middle-age |

# BONE DISORDERS: LAB VALUES

| Disorder | Calcium | Phosphate | ALP | PTH |
|---|---|---|---|---|
| **Osteoporosis** | Normal | Normal | Normal | Normal |
| **Osteomalacia** | Decreased | Decreased | Increased | Increased |
| **Primary hyperparathyroidism** (→ osteitis fibrosa cystica) | Increased | Decreased | Increased | Increased |
| **Chronic kidney disease** (→ secondary hyperparathyroidism) | Decreased | Increased | Increased | Increased |
| **Paget's disease** | Normal | Normal | Increased | Normal |
| **Osteopetrosis** | Normal | Normal | Normal | Normal |

# TUMOUR NECROSIS FACTOR

Tumour necrosis factor (TNF) is a pro-inflammatory cytokine with multiple roles in the immune system

TNF is secreted mainly by macrophages and has a number of effects on the immune system, acting mainly in a paracrine fashion:
- activates macrophages and neutrophils
- acts as costimulator for T cell activation
- key mediator of bodies response to Gram negative septicaemia
- similar properties to IL-1
- anti-tumour effect (e.g. phospholipase activation)

TNF-alpha binds to both the p55 and p75 receptor. These receptors can induce apoptosis. It also cause activation of NFkB

Endothelial effects include increase expression of selectins and increased production of platelet activating factor, IL-1 and prostaglandins

TNF promotes the proliferation of fibroblasts and their production of protease and collagenase. It is thought fragments of receptors act as binding points in serum

Systemic effects include pyrexia, increased acute phase proteins and disordered metabolism leading to cachexia

TNF is important in the pathogenesis of rheumatoid arthritis - TNF blockers (e.g. infliximab, etanercept) are now licensed for treatment of severe rheumatoid

TNF blockers
- infliximab: monoclonal antibody, IV administration
- etanercept: fusion protein that mimics the inhibitory effects of naturally occurring soluble TNF receptors, subcutaneous administration
- adalimumab: monoclonal antibody, subcutaneous administration
- adverse effects of TNF blockers include reactivation of latent tuberculosis and demyelination

Infliximab is also used in active Crohn's disease unresponsive to steroids

# AZATHIOPRINE

Azathioprine is metabolised to the active compound mercaptopurine, a purine analogue that inhibits purine synthesis. A thiopurine methyltransferase (TPMT) test may be needed to look for individuals prone to azathioprine toxicity.

Adverse effects include

- bone marrow depression
- nausea/vomiting
- pancreatitis
- increased risk of non-melanoma skin cancer

A significant interaction may occur with allopurinol and hence lower doses of azathioprine should be used.

Azathioprine is generally considered safe to use in pregnancy.

# MYCOPHENOLATE MOFETIL

Mode of action

- inhibits inosine monophosphate dehydrogenase, which is needed for purine synthesis
- as T and B cells are particularly dependent on this pathway it can reduce proliferation of immune cells

# CHRONIC FATIGUE SYNDROME

Diagnosed after at least 4 months of disabling fatigue affecting mental and physical function more than 50% of the time in the absence of other disease which may explain symptoms

Epidemiology
- more common in females
- past psychiatric history has not been shown to be a risk factor

Fatigue is the central feature, other recognised features include
- sleep problems, such as insomnia, hypersomnia, unrefreshing sleep, a disturbed sleep-wake cycle
- muscle and/or joint pains
- headaches
- painful lymph nodes without enlargement
- sore throat
- cognitive dysfunction, such as difficulty thinking, inability to concentrate, impairment of short-term memory, and difficulties with word-finding
- physical or mental exertion makes symptoms worse
- general malaise or 'flu-like' symptoms
- dizziness
- nausea
- palpitations

Investigation
- NICE guidelines suggest carrying out a large number of screening blood tests to exclude other pathology e.g. FBC, U&E, LFT, glucose, TFT, ESR, CRP, calcium, CK, ferritin*, coeliac screening and also urinalysis

Management
- cognitive behaviour therapy - very effective, number needed to treat = 2
- graded exercise therapy - a formal supervised program, not advice to go to the gym
- 'pacing' - organising activities to avoid tiring
- low-dose amitriptyline may be useful for poor sleep
- referral to a pain management clinic if pain is a predominant feature

Better prognosis in children

*children and young people only

# DERMATOMYOSITIS

Overview
- an inflammatory disorder causing symmetrical, proximal muscle weakness and characteristic skin lesions
- may be idiopathic or associated with connective tissue disorders or underlying malignancy (typically ovarian, breast and lung cancer, found in 20-25% - more if patient older). Screening for an underlying malignancy is usually performed following a diagnosis of dermatomyositis
- polymyositis is a variant of the disease where skin manifestations are not prominent

Skin features
- photosensitive
- macular rash over back and shoulder
- heliotrope rash in the periorbital region
- Gottron's papules - roughened red papules over extensor surfaces of fingers
- 'mechanic's hands': extremely dry and scaly hands with linear 'cracks' on the palmar and lateral aspects of the fingers
- nail fold capillary dilatation

Other features
- proximal muscle weakness +/- tenderness
- Raynaud's
- respiratory muscle weakness
- interstitial lung disease: e.g. Fibrosing alveolitis or organising pneumonia
- dysphagia, dysphonia

Investigations
- the majority of patients (around 80%) are ANA positive
- around 30% of patients have antibodies to aminoacyl-tRNA synthetases (anti-synthetase antibodies), including:
  - antibodies against histidine-tRNA ligase (also called Jo-1)
  - antibodies to signal recognition particle (SRP)
  - anti-Mi-2 antibodies

# DERMATOMYOSITIS: INVESTIGATIONS AND MANAGEMENT

Investigations
- elevated creatine kinase
- EMG
- muscle biopsy
- ANA positive in 60%
- anti-Mi-2 antibodies are highly specific for dermatomyositis, but are only seen in around 25% of patients

- anti-Jo-1 antibodies are not commonly seen in dermatomyositis - they are more common in polymyositis where they are seen in a pattern of disease associated with lung involvement, Raynaud's and fever

Management
- prednisolone

# POLYMYOSITIS

Overview
- inflammatory disorder causing symmetrical, proximal muscle weakness
- thought to be a T-cell mediated cytotoxic process directed against muscle fibres
- may be idiopathic or associated with connective tissue disorders
- associated with malignancy
- dermatomyositis is a variant of the disease where skin manifestations are prominent, for example a purple (heliotrope) rash on the cheeks and eyelids
- typically affects middle-aged, female:male 3:1

Features
- proximal muscle weakness +/- tenderness
- Raynaud's
- respiratory muscle weakness
- interstitial lung disease: e.g. fibrosing alveolitis or organising pneumonia
- dysphagia, dysphonia

Investigations
- elevated creatine kinase
- other muscle enzymes (lactate dehydrogenase (LD), aldolase, AST and ALT) are also elevated in 85-95% of patients
- EMG
- muscle biopsy
- anti-synthetase antibodies
  - anti-Jo-1 antibodies are seen in pattern of disease associated with lung involvement, Raynaud's and fever

# POLYMYALGIA RHEUMATICA

Polymyalgia rheumatica (PMR) is a relatively common condition seen in older people characterised by muscle stiffness and raised inflammatory markers. Whilst it appears to be closely related to temporal arteritis the underlying cause is not fully understood and it does not appear to be a vasculitic process.

Features
- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- aching, morning stiffness in proximal limb muscles
- weakness is not considered a symptom of polymyalgia rheumatica
- also mild polyarthralgia, lethargy, depression, low-grade fever, anorexia, night sweats

Investigations
- raised inflammatory markers e.g. ESR > 40 mm/hr
- note creatine kinase and EMG normal

Treatment
- prednisolone e.g. 15mg/od
  - patients typically respond dramatically to steroids, failure to do so should prompt consideration of an alternative diagnosis

# FIBROMYALGIA

Fibromyalgia is a syndrome characterised by widespread pain throughout the body with tender points at specific anatomical sites. The cause of fibromyalgia is unknown.

Epidemiology
- women are around 5 times more likely to be affected
- typically presents between 30-50 years old

Features
- chronic pain: at multiple site, sometimes 'pain all over'
- lethargy
- cognitive impairment: 'fibro fog'
- sleep disturbance, headaches, dizziness are common

Diagnosis is clinical and sometimes refers to the American College of Rheumatology classification criteria which lists 9 pairs of tender points on the body. If a patient is tender in at least 11 of these 18 points it makes a diagnosis of fibromyalgia more likely

The management of fibromyalgia is often difficult and needs to be tailored to the individual patient. A psychosocial and multidisciplinary approach is helpful. Unfortunately there is currently a paucity of evidence and guidelines to guide practice. The following is partly based on consensus guidelines from the European League against Rheumatism (EULAR) published in 2007 and also a BMJ review in 2014.

- explanation
- aerobic exercise: has the strongest evidence base
- cognitive behavioural therapy
- medication: pregabalin, duloxetine, amitriptyline

# MYOPATHIES

Features

- symmetrical muscle weakness (proximal > distal)
- common problems are rising from chair or getting out of bath
- sensation normal, reflexes normal, no fasciculation

Causes

- inflammatory: polymyositis
- inherited: Duchenne/Becker muscular dystrophy, myotonic dystrophy
- endocrine: Cushing's, thyrotoxicosis
- alcohol

# ANCA

There are two main types of anti-neutrophil cytoplasmic antibodies (ANCA) - cytoplasmic (cANCA) and perinuclear (pANCA)

For the exam, remember:
- cANCA - granulomatosis with polyangiitis (Wegener's granulomatosis)
- pANCA - Churg-Strauss syndrome + others (see below)

cANCA
- most common target serine proteinase 3 (PR3)
- some correlation between cANCA levels and disease activity
- granulomatosis with polyangiitis, positive in > 90%
- microscopic polyangiitis, positive in 40%

pANCA
- most common target is myeloperoxidase (MPO)
- cannot use level of pANCA to monitor disease activity
- associated with immune crescentic glomerulonephritis (positive in c. 80% of patients)
- microscopic polyangiitis, positive in 50-75%
- Churg-Strauss syndrome, positive in 60%
- primary sclerosing cholangitis, positive in 60-80%
- granulomatosis with polyangiitis, positive in 25%

Other causes of positive ANCA (usually pANCA)
- inflammatory bowel disease (UC > Crohn's)
- connective tissue disorders: RA, SLE, Sjogren's
- autoimmune hepatitis

# EXTRACTABLE NUCLEAR ANTIGENS

Overview
- specific nuclear antigens
- usually associated with being ANA positive

Examples
- anti-Ro: Sjogren's syndrome, SLE, congenital heart block
- anti-La: Sjogren's syndrome
- anti-Jo 1: polymyositis
- anti-scl-70: diffuse cutaneous systemic sclerosis
- anti-centromere: limited cutaneous systemic sclerosis

# SYSTEMIC LUPUS ERYTHEMATOSUS

Epidemiology

- much more common in females (F:M = 9:1)
- more common in Afro-Caribbeans* and Asian communities
- onset is usually 20-40 years
- incidence has risen substantially during the past 50 years (3 fold using American College of Rheumatology criteria)

Pathophysiology

- autoimmune disease: SLE a type 3 hypersensitivity reaction
- associated with HLA B8, DR2, DR3
- thought to be caused by immune system dysregulation leading to immune complex formation
- immune complex deposition can affect any organ including the skin, joints, kidneys and brain

*It is said the incidence in black Africans is much lower than in black Americans - the reasons for this are unclear

# SYSTEMIC LUPUS ERYTHEMATOSUS: FEATURES

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disorder. It typically presents in early adulthood and is more common in women and people of Afro-Caribbean origin.

General features

- fatigue
- fever
- mouth ulcers
- lymphadenopathy

Skin

- malar (butterfly) rash: spares nasolabial folds
- discoid rash: scaly, erythematous, well demarcated rash in sun-exposed areas. Lesions may progress to become pigmented and hyperkeratotic before becoming atrophic
- photosensitivity
- Raynaud's phenomenon
- livedo reticularis
- non-scarring alopecia

Musculoskeletal

- arthralgia
- non-erosive arthritis

Cardiovascular

- pericarditis: the most common cardiac manifestation
- myocarditis

Respiratory

- pleurisy
- fibrosing alveolitis

Renal

- proteinuria
- glomerulonephritis (diffuse proliferative glomerulonephritis is the most common type)

Neuropsychiatric

- anxiety and depression
- psychosis
- seizures

# SYSTEMIC LUPUS ERYTHEMATOSUS: INVESTIGATIONS

Antibodies

- 99% are ANA positive
  - this high sensitivity makes it a useful rule out test, but it has low specificity
- 20% are rheumatoid factor positive
- anti-dsDNA: highly specific (> 99%), but less sensitive (70%)
- anti-Smith: highly specific (> 99%), sensitivity (30%)
- also: anti-U1 RNP, SS-A (anti-Ro) and SS-B (anti-La)

Monitoring

- inflammatory markers
  - ESR is generally used
  - during active disease the CRP is characteristically normal - a raised CRP may indicate underlying infection
- complement levels (C3, C4) are low during active disease (formation of complexes leads to consumption of complement)
- anti-dsDNA titres can be used for disease monitoring (but note not present in all patients)

# SYSTEMIC LUPUS ERYTHEMATOSUS: PREGNANCY

Overview
- risk of maternal autoantibodies crossing the placenta
- leads to a condition termed neonatal lupus erythematosus
- neonatal complications include congenital heart block
- strongly associated withanti-Ro (SSA) antibodies

# SYSTEMIC SCLEROSIS

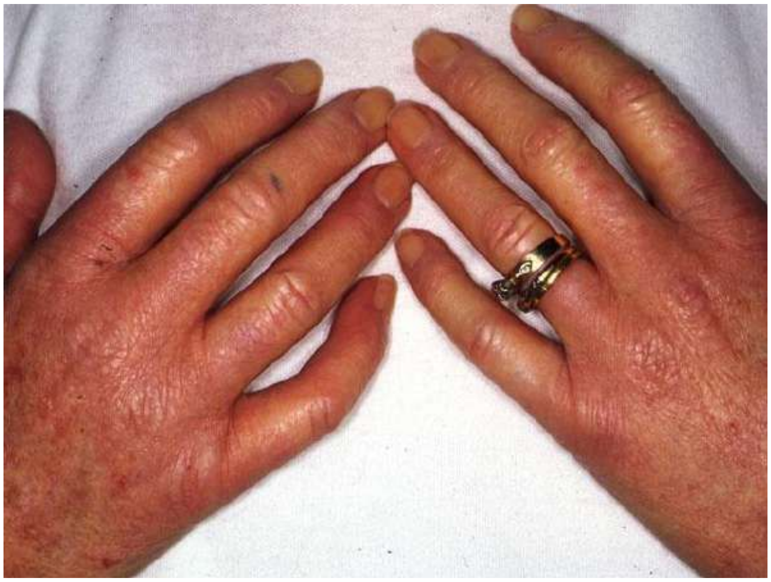
Systemic sclerosis is a condition of unknown aetiology characterised by hardened, sclerotic skin and other connective tissues. It is four times more common in females.

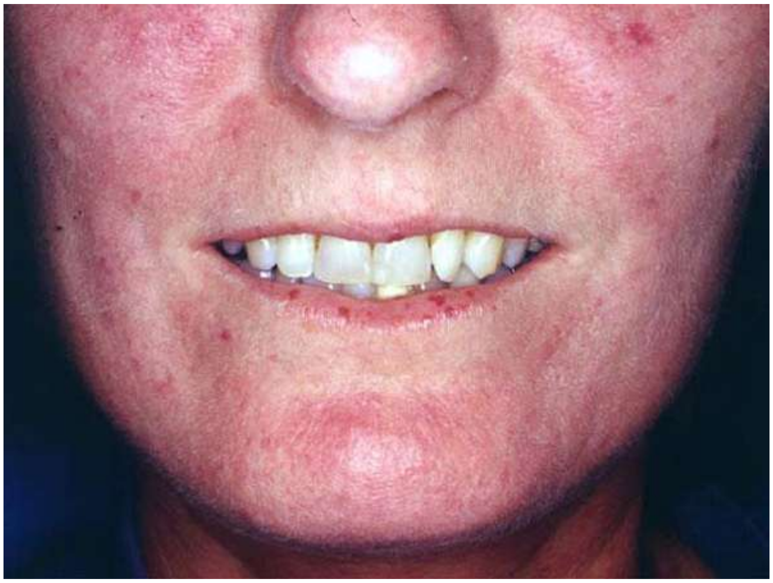
There are three patterns of disease:

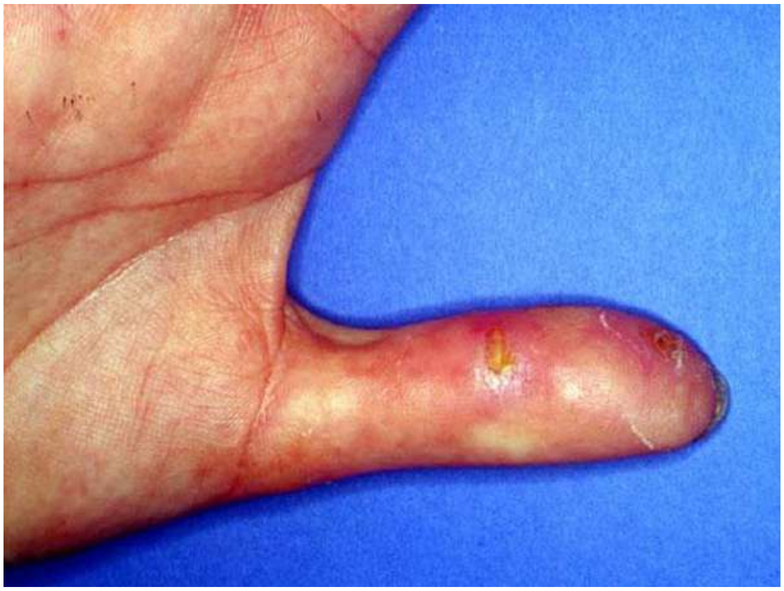
Limited cutaneous systemic sclerosis
- Raynaud's may be first sign
- scleroderma affects face and distal limbs predominately
- associated with anti-centromere antibodies
- a subtype of limited systemic sclerosis is CREST syndrome: Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia

Diffuse cutaneous systemic sclerosis
- scleroderma affects trunk and proximal limbs predominately
- associated with scl-70 antibodies
- the most common cause of death is now respiratory involvement, which is seen in around 80%: interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH)
- other complications include renal disease and hypertension
- poor prognosis

Scleroderma (without internal organ involvement)
- tightening and fibrosis of skin
- may be manifest as plaques (morphoea) or linear







Antibodies

- ANA positive in 90%
- RF positive in 30%
- anti-scl-70 antibodies associated with diffuse cutaneous systemic sclerosis
- anti-centromere antibodies associated with limited cutaneous systemic sclerosis

# RAYNAUD'S

Raynaud's phenomena may be primary (Raynaud's disease) or secondary (Raynaud's phenomenon)

Raynaud's disease typically presents in young women (e.g. 30 years old) with bilateral symptoms.

Factors suggesting underlying connective tissue disease

- onset after 40 years
- unilateral symptoms
- rashes
- presence of autoantibodies
- features which may suggest rheumatoid arthritis or SLE, for example arthritis or recurrent miscarriages
- digital ulcers, calcinosis
- very rarely: chilblains

Secondary causes

  - connective tissue disorders: scleroderma (most common), rheumatoid arthritis, SLE
  - leukaemia
  - type I cryoglobulinaemia, cold agglutinins
  - use of vibrating tools
  - drugs: oral contraceptive pill, ergot
  - cervical rib

Management

- all patients with suspected secondary Raynaud's phenomenon should be referred to secondary care
- first-line: calcium channel blockers e.g. nifedipine
- IV prostacyclin (epoprostenol) infusions: effects may last several weeks/months

# DISCOID LUPUS ERYTHEMATOUS

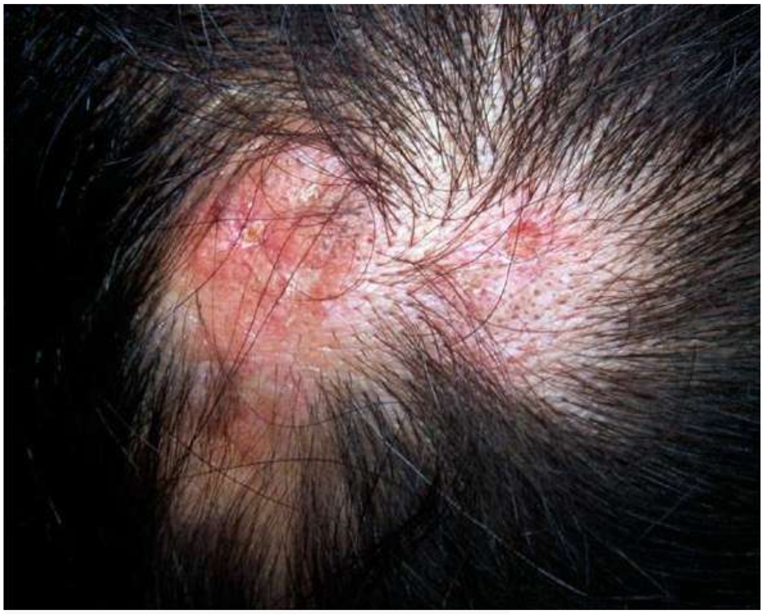
Discoid lupus erythematosus is a benign disorder generally seen in younger females. It very rarely progresses to systemic lupus erythematosus (in less than 5% of cases). Discoid lupus erythematosus is characterised by follicular keratin plugs and is thought to be autoimmune in aetiology

Features

- erythematous, raised rash, sometimes scaly
- may be photosensitive
- more common on face, neck, ears and scalp
- lesions heal with atrophy, scarring (may cause scarring alopecia), and pigmentation

Management

- topical steroid cream
- oral antimalarials may be used second-line e.g. hydroxychloroquine
- avoid sun exposure



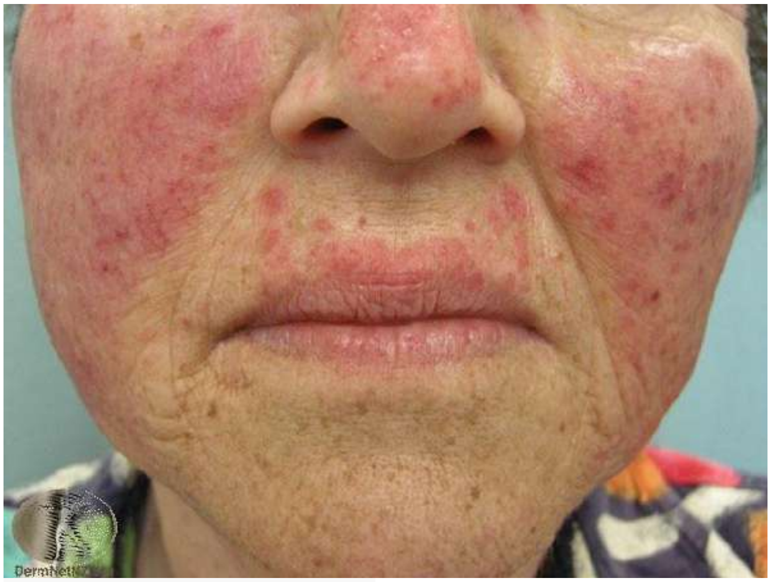
Discoid lupus erythematous affecting the scalp

# DRUG-INDUCED LUPUS

In drug-induced lupus not all the typical features of systemic lupus erythematosus are seen, with renal and nervous system involvement being unusual. It usually resolves on stopping the drug.

Features

- arthralgia
- myalgia
- skin (e.g. malar rash) and pulmonary involvement (e.g. pleurisy) are common
- ANA positive in 100%, dsDNA negative
- anti-histone antibodies are found in 80-90%
- anti-Ro, anti-Smith positive in around 5%



A woman with drug-induced lupus

Most common causes

- procainamide
- hydralazine

Less common causes

- isoniazid
- minocycline
- phenytoin

# SJOGREN'S SYNDROME

Sjogren's syndrome is an autoimmune disorder affecting exocrine glands resulting in dry mucosal surfaces. It may be primary (PSS) or secondary to rheumatoid arthritis or other connective tissue disorders, where it usually develops around 10 years after the initial onset. Sjogren's syndrome is much more common in females (ratio 9:1). There is a marked increased risk of lymphoid malignancy (40-60 fold).

Features

- dry eyes: keratoconjunctivitis sicca
- dry mouth
- vaginal dryness
- arthralgia
- Raynaud's, myalgia
- sensory polyneuropathy
- recurrent episodes of parotitis
- renal tubular acidosis (usually subclinical)

Investigation

- rheumatoid factor (RF) positive in nearly 100% of patients
- ANA positive in 70%
- anti-Ro (SSA) antibodies in 70% of patients with PSS
- anti-La (SSB) antibodies in 30% of patients with PSS
- Schirmer's test: filter paper near conjunctival sac to measure tear formation
- histology: focal lymphocytic infiltration
- also: hypergammaglobulinaemia, low C4

Management

- artificial saliva and tears
- pilocarpine may stimulate saliva production

# MIXED CONNECTIVE TISSUE DISEASE

Mixed connective tissue disease (MCTD, Sharp's syndrome) is a rare, heterogeneous, multi-system autoimmune disorder. It is a distinct clinical entity, but features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and myositis may all be present. It is associated with anti-U1 ribonucleoprotein (RNP) antibodies.* It is not to be confused with 'undifferentiated connective tissue disease'.**

Epidemiology

- Male:female ratio 1:3
- Average age of presentation 30-40, may present in children
- Rare - incidence in adult population is estimated to be 2.1/million/year in one Norwegian study

Presentation:

- Raynaud's phenomenon often precedes other symptoms and occurs in 90% of cases
- Polyarthralgia/arthritis
- Myalgia
- 'Sausage fingers'(dactylitis)

Other clinically important features:

- Dermatological: photosensitive rash, scleroderma-like changes, alopecia
- Oesophageal dysfunction
- Respiratory: pleuritis, pulmonary hypertension, interstitial lung disease
- Haematological: anaemia, lymphadenopathy, splenomegaly, rarely TTP
- Cardiac: pericarditis, pericardial effusion, accelerated coronary artery disease
- Renal: glomerulonephritis (tends to be milder than SLE)
- Neuropsychiatric: seizures, mood disturbance

Investigations:

- Exclude other connective tissue disease/vasculitis
- Bloods FBC: anaemia, leucopenia, thrombocytopenia, U+E: renal impairment, CRP/ESR raised
- ANA (usually) positive, anti Ds-DNA and scleroderma-specific antibodies (e.g. Anti-Scl70) are negative
- Anti-U1 RNP (an extractable nuclear antigen, ENA), must be positive*.
- Organ-specific investigations, e.g. ECG, echo, CT chest, MRI brain

Management:

- No large-scale trials - patients have been included in trials for SLE/SSc and show similar levels of response to immunosuppression/DMARDs
- Calcium channel blockers may be used for the treatment of Raynaud's
- Proton pump inhibitors for reflux disease
- Endothelin receptor antagonists/prostacyclin analogues in pulmonary hypertension
- Smoking cessation, moderate exercise

Prognosis:

- 1/3 long-term remission, 1/3 have chronic symptoms, 1/3 develop severe systemic involvement and premature death.

*Note that anti-U1 RNP antibodies are not completely specific and may also be seen in definite SSc and SLE
**Undifferentiated connective tissue disease refers to syndromes in which features of one or more 'classical' connective tissue disease may be present, but do not meet diagnostic criteria. Anti-U1 RNP is absent.

# MARFAN'S SYNDROME

Marfan's syndrome is an autosomal dominant connective tissue disorder. It is caused by a defect in the FBN1 gene on chromosome 15 that codes for the protein fibrillin-1. It affects around 1 in 3,000 people.

Features

- tall stature with arm span to height ratio > 1.05
- high-arched palate
- arachnodactyly
- pectus excavatum
- pes planus
- scoliosis of > 20 degrees
- heart: dilation of the aortic sinuses (seen in 90%) which may lead to aortic aneurysm, aortic dissection, aortic regurgitation, mitral valve prolapse (75%),
- lungs: repeated pneumothoraces

- eyes: upwards lens dislocation (superotemporal ectopia lentis), blue sclera, myopia
- dural ectasia (ballooning of the dural sac at the lumbosacral level)

The life expectancy of patients used to be around 40-50 years. With the advent of regular echocardiography monitoring and beta-blocker/ACE-inhibitor therapy this has improved significantly over recent years. Aortic dissection and other cardiovascular problems remain the leading cause of death however.

# EHLER-DANLOS SYNDROME

Ehler-Danlos syndrome is an autosomal dominant connective tissue disorder that mostly affects type III collagen. This results in the tissue being more elastic than normal leading to joint hypermobility and increased elasticity of the skin.

Features and complications
- elastic, fragile skin
- joint hypermobility: recurrent joint dislocation
- easy bruising
- aortic regurgitation, mitral valve prolapse and aortic dissection
- subarachnoid haemorrhage
- angioid retinal streaks

# RHEUMATOID ARTHRITIS: EPIDEMIOLOGY

Epidemiology
- peak onset = 30-50 years, although occurs in all age groups
- F:M ratio = 3:1
- prevalence = 1%
- some ethnic differences e.g. high in Native Americans
- associated with HLA-DR4 (especially Felty's syndrome)

# RHEUMATOID ARTHRITIS: ANTIBODIES

**Rheumatoid factor**
Rheumatoid factor (RF) is a circulating antibody (usually IgM) which reacts with the Fc portion of the patients own IgG.

RF can be detected by either
- Rose-Waaler test: sheep red cell agglutination
- Latex agglutination test (less specific)

RF is positive in 70-80% of patients with rheumatoid arthritis, high titre levels are associated with severe progressive disease (but NOT a marker of disease activity)

Other conditions associated with a positive RF include:
- Sjogren's syndrome (around 100%)
- Felty's syndrome (around 100%)
- infective endocarditis (= 50%)
- SLE (= 20-30%)
- systemic sclerosis (= 30%)
- general population (= 5%)
- rarely: TB, HBV, EBV, leprosy

**Anti-cyclic citrullinated peptide antibody**
Anti-cyclic citrullinated peptide antibody may be detectable up to 10 years before the development of rheumatoid arthritis. It may therefore play a key role in the future of rheumatoid arthritis, allowing early detection of patients suitable for aggressive anti-TNF therapy. It has a sensitivity similar to rheumatoid factor (around 70%) with a much higher specificity of 90-95%.

NICE recommends that patients with suspected rheumatoid arthritis who are rheumatoid factor negative should be test for anti-CCP antibodies.

## RHEUMATOID ARTHRITIS: PRESENTATION

Typical features
- swollen, painful joints in hands and feet
- stiffness worse in the morning
- gradually gets worse with larger joints becoming involved
- presentation usually insidiously develops over a few months
- positive 'squeeze test' - discomfort on squeezing across the metacarpal or metatarsal joints

Swan neck and boutonnière deformities are late features of rheumatoid arthritis and unlikely to be present in a recently diagnosed patient.

Other presentations:
- acute onset with marked systemic disturbance
- relapsing/remitting monoarthritis of different large joints (palindromic rheumatism)

## RHEUMATOID ARTHRITIS: DIAGNOSIS

NICE have stated that clinical diagnosis is more important than criteria such as those defined by the American College of Rheumatology.

2010 American College of Rheumatology criteria

Target population. Patients who
1) have at least 1 joint with definite clinical synovitis
2) with the synovitis not better explained by another disease

Classification criteria for rheumatoid arthritis (add score of categories A-D;
a score of 6/10 is needed definite rheumatoid arthritis)

Key
RF = rheumatoid factor
ACPA = anti-cyclic citrullinated peptide antibody

| Factor | Scoring | |
|---|---|---|
| **A. Joint involvement** | | |
| | 1 large joint | 0 |
| | 2 - 10 large joints | 1 |
| | 1 - 3 small joints (with or without involvement of large joints) | 2 |
| | 4 - 10 small joints (with or without involvement of large joints) | 3 |

| Factor | Scoring | |
|---|---|---|
| | 10 joints (at least 1 small joint) | 5 |
| **B. Serology (at least 1 test result is needed for classification)** | | |
| | Negative RF and negative ACPA | 0 |
| | Low-positive RF or low-positive ACPA | 2 |
| | High-positive RF or high-positive ACPA | 3 |
| **C. Acute-phase reactants (at least 1 test result is needed for classification)** | | |
| | Normal CRP and normal ESR | 0 |
| | Abnormal CRP or abnormal ESR | 1 |
| **D. Duration of symptoms** | | |
| | < 6 weeks | 0 |
| | > 6 weeks | 1 |

## RHEUMATOID ARTHRITIS: X-RAY CHANGES

Early x-ray findings
- loss of joint space
- juxta-articular osteoporosis
- soft-tissue swelling

Late x-ray findings
- periarticular erosions
- subluxation

## RHEUMATOID ARTHRITIS: MANAGEMENT

The management of rheumatoid arthritis (RA) has been revolutionised by the introduction of disease-modifying therapies in the past decade.

Patients with evidence of joint inflammation should start a combination of disease-modifying drugs (DMARD) as soon as possible. Other important treatment options include analgesia, physiotherapy and surgery.

Initial therapy
- In 2018 NICE updated their rheumatoid arthritis guidelines. They now recommend DMARD **monotherapy** +/- a short-course of bridging prednisolone. In the past dual DMARD therapy was advocated as the initial step.

Monitoring response to treatment

- NICE recommends using a combination of CRP and disease activity (using a composite score such as DAS28) to assess response to treatment

Flares
- flares of RA are often managed with corticosteroids - oral or intramuscular

DMARDs
- methotrexate is the most widely used DMARD. Monitoring of FBC & LFTs is essential due to the risk of myelosuppression and liver cirrhosis. Other important side-effects include pneumonitis
- sulfasalazine
- leflunomide
- hydroxychloroquine

TNF-inhibitors
- the current indication for a TNF-inhibitor is an inadequate response to at least two DMARDs including methotrexate
- etanercept: recombinant human protein, acts as a decoy receptor for TNF-α, subcutaneous administration, can cause demyelination, risks include reactivation of tuberculosis
- infliximab: monoclonal antibody, binds to TNF-α and prevents it from binding with TNF receptors, intravenous administration, risks include reactivation of tuberculosis
- adalimumab: monoclonal antibody, subcutaneous administration

Rituximab
- anti-CD20 monoclonal antibody, results in B-cell depletion
- two 1g intravenous infusions are given two weeks apart
- infusion reactions are common

Abatacept
- fusion protein that modulates a key signal required for activation of T lymphocytes
- leads to decreased T-cell proliferation and cytokine production
- given as an infusion
- not currently recommend by NICE

# LEFLUNOMIDE

Leflunomide is a disease modifying anti-rheumatic drug (DMARD) mainly used in the management of rheumatoid arthritis. It has a very long half-life which should be remembered considering it's teratogenic potential.

Contraindications

- pregnancy - the BNF advises: *'Effective contraception essential during treatment and for at least 2 years after treatment in women and at least 3 months after treatment in men (plasma concentration monitoring required'*
- caution should also be exercised with pre-existing lung and liver disease

Adverse effects
- gastrointestinal, especially diarrhoea
- hypertension
- weight loss/anorexia
- peripheral neuropathy
- myelosuppression
- pneumonitis

Monitoring
- FBC/LFT and blood pressure

Stopping
- leflunomide has a very long wash-out period of up to a year which requires co-administration of cholestyramine

## HYDROXYCHLOROQUINE

Hydroxychloroquine is used in the management of rheumatoid arthritis and systemic/discoid lupus erythematosus. It is pharmacologically very similar to chloroquine which is used to treat certain types of malaria.

Adverse effects
- bull's eye retinopathy - may result in severe and permanent visual loss
  - recent data suggest that retinopathy caused by hydroxychloroquine is more common than previously thought and the most recent RCOphth guidelines (March 2018) suggest colour retinal photography and spectral domain optical coherence tomography scanning of the macula
  - baseline ophthalmological examination and annual screening is generally recommened

A contrast to many drugs used in rheumatology, hydroxychloroquine may be used if needed in pregnant women.

Monitoring
- the BNF advises: *'Ask patient about visual symptoms and monitor visual acuity annually using the standard reading chart'*

## METHOTREXATE

Methotrexate is an antimetabolite that inhibits dihydrofolate reductase, an enzyme essential for the synthesis of purines and pyrimidines. It is considered an 'important' drug as whilst it can be very effective in controlling disease the side-effects may be potentially life-threatening - careful prescribing and close monitoring is essential.

Indications
- inflammatory arthritis, especially rheumatoid arthritis
- psoriasis
- some chemotherapy acute lymphoblastic leukaemia

Adverse effects
- mucositis
- myelosuppression
- pneumonitis
- pulmonary fibrosis
- liver fibrosis
- mucositis

Pregnancy
- women should avoid pregnancy for at least 6 months after treatment has stopped
- the BNF also advises that men using methotrexate need to use effective contraception for at least 6 months after treatment

Prescribing methotrexate
- methotrexate is a drug with a high potential for patient harm. It is therefore important that you are familiar with guidelines relating to its use
- methotrexate is taken weekly, rather than daily
- FBC, U&E and LFTs need to be regularly monitored. The Committee on Safety of Medicines recommend 'FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months'
- folic acid 5mg once weekly should be co-prescribed, taken more than 24 hours after methotrexate dose
- the starting dose of methotrexate is 7.5 mg weekly (source: BNF)
- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)

Interactions
- avoid prescribing trimethoprim or co-trimoxazole concurrently - increases risk of marrow aplasia
- high-dose aspirin increases the risk of methotrexate toxicity secondary to reduced excretion

Methotrexate toxicity
- the treatment of choice is folinic acid

# SULFASALAZINE

Sulfasalazine is a disease modifying anti-rheumatic drug (DMARDs) used in the management of inflammatory arthritis, especially rheumatoid arthritis. It is also used in the management of inflammatory bowel disease.

Sulfasalazine is a prodrug for 5-ASA which works through decreasing neutrophil chemotaxis alongside suppressing proliferation of lymphocytes and pro-inflammatory cytokines.

Cautions

- G6PD deficiency
- allergy to aspirin or sulphonamides (cross-sensitivity)

Adverse effects

- oligospermia
- Stevens-Johnson syndrome
- pneumonitis / lung fibrosis
- myelosuppression, Heinz body anaemia, megaloblastic anaemia
- may colour tears → stained contact lenses

In contrast to other DMARDs, sulfasalazine is considered safe to use in both pregnancy and breastfeeding.

# RHEUMATOID ARTHRITIS: DRUG SIDE-EFFECTS

The table below lists some of the characteristic (if not common) side-effects of drugs used to treat rheumatoid arthritis:

| Drug | Side-effects |
|---|---|
| Methotrexate | Myelosuppression<br>Liver cirrhosis<br>Pneumonitis |
| Sulfasalazine | Rashes<br>Oligospermia<br>Heinz body anaemia<br>Interstitial lung disease |
| Leflunomide | Liver impairment<br>Interstitial lung disease<br>Hypertension |
| Hydroxychloroquine | Retinopathy<br>Corneal deposits |
| Prednisolone | Cushingoid features<br>Osteoporosis<br>Impaired glucose tolerance |

| Drug | Side-effects |
|---|---|
|  | Hypertension<br>Cataracts |
| Gold | Proteinuria |
| Penicillamine | Proteinuria<br>Exacerbation of myasthenia gravis |
| Etanercept | Demyelination<br>Reactivation of tuberculosis |
| Infliximab | Reactivation of tuberculosis |
| Adalimumab | Reactivation of tuberculosis |
| Rituximab | Infusion reactions are common |
| NSAIDs (e.g. naproxen, ibuprofen) | Bronchospasm in asthmatics<br>Dyspepsia/peptic ulceration |

# RHEUMATOID ARTHRITIS: PROGNOSTIC FEATURES

A number of features have been shown to predict a poor prognosis in patients with rheumatoid arthritis, as listed below

Poor prognostic features
- rheumatoid factor positive
- poor functional status at presentation
- HLA DR4
- X-ray: early erosions (e.g. after < 2 years)
- extra articular features e.g. nodules
- insidious onset
- anti-CCP antibodies

In terms of gender there seems to be a split in what the established sources state is associated with a poor prognosis. However both the American College of Rheumatology and the recent NICE guidelines (which looked at a huge number of prognosis studies) seem to conclude that female gender is associated with a poor prognosis.

# RHEUMATOID ARTHRITIS: PREGNANCY

Rheumatoid arthritis (RA) typically develops in women of a reproductive age. Issues surrounding conception are therefore commonly encountered. There are no current published guidelines regarding how patients considering conception should be managed although expert reviews are largely in agreement.

Key points

- patients with early or poorly controlled RA should be advised to defer conception until their disease is more stable
- RA symptoms tend to improve in pregnancy but only resolve in a small minority. Patients tend to have a flare following delivery
- methotrexate is not safe in pregnancy and needs to be stopped at least 6 months before conception
- leflunomide is not safe in pregnancy
- sulfasalazine and hydroxychloroquine are considered safe in pregnancy
- interestingly studies looking at pregnancy outcomes in patients treated with TNF-α blockers do not show any significant increase in adverse outcomes. It should be noted however that many of the patients included in the study stopped taking TNF-α blockers when they found out they were pregnant
- low-dose corticosteroids may be used in pregnancy to control symptoms
- NSAIDs may be used until 32 weeks but after this time should be withdrawn due to the risk of early close of the ductus arteriosus
- patients should be referred to an obstetric anaesthetist due to the risk of atlanto-axial subluxation

## RHEUMATOID ARTHRITIS: COMPLICATIONS

A wide variety of extra-articular complications occur in patients with rheumatoid arthritis (RA):

- respiratory: pulmonary fibrosis, pleural effusion, pulmonary nodules, bronchiolitis obliterans, methotrexate pneumonitis, pleurisy
- ocular: keratoconjunctivitis sicca (most common), episcleritis, scleritis, corneal ulceration, keratitis, steroid-induced cataracts, chloroquine retinopathy
- osteoporosis
- ischaemic heart disease: RA carries a similar risk to type 2 diabetes mellitus
- increased risk of infections
- depression

Less common

- Felty's syndrome (RA + splenomegaly + low white cell count)
- amyloidosis

# TEMPORAL ARTERITIS

Temporal arteritis is large vessel vasculitis which overlaps with polymyalgia rheumatica (PMR). Histology shows changes which characteristically 'skips' certain sections of affected artery whilst damaging others.

Features
- typically patient > 60 years old
- usually rapid onset (e.g. < 1 month)
- headache (found in 85%)
- jaw claudication (65%)
- visual disturbances secondary to anterior ischemic optic neuropathy
- tender, palpable temporal artery
- around 50% have features of PMR: aching, morning stiffness in proximal limb muscles (not weakness)
- also lethargy, depression, low-grade fever, anorexia, night sweats

Investigations
- raised inflammatory markers: ESR > 50 mm/hr (note ESR < 30 in 10% of patients). CRP may also be elevated
- temporal artery biopsy: skip lesions may be present
- note creatine kinase and EMG normal

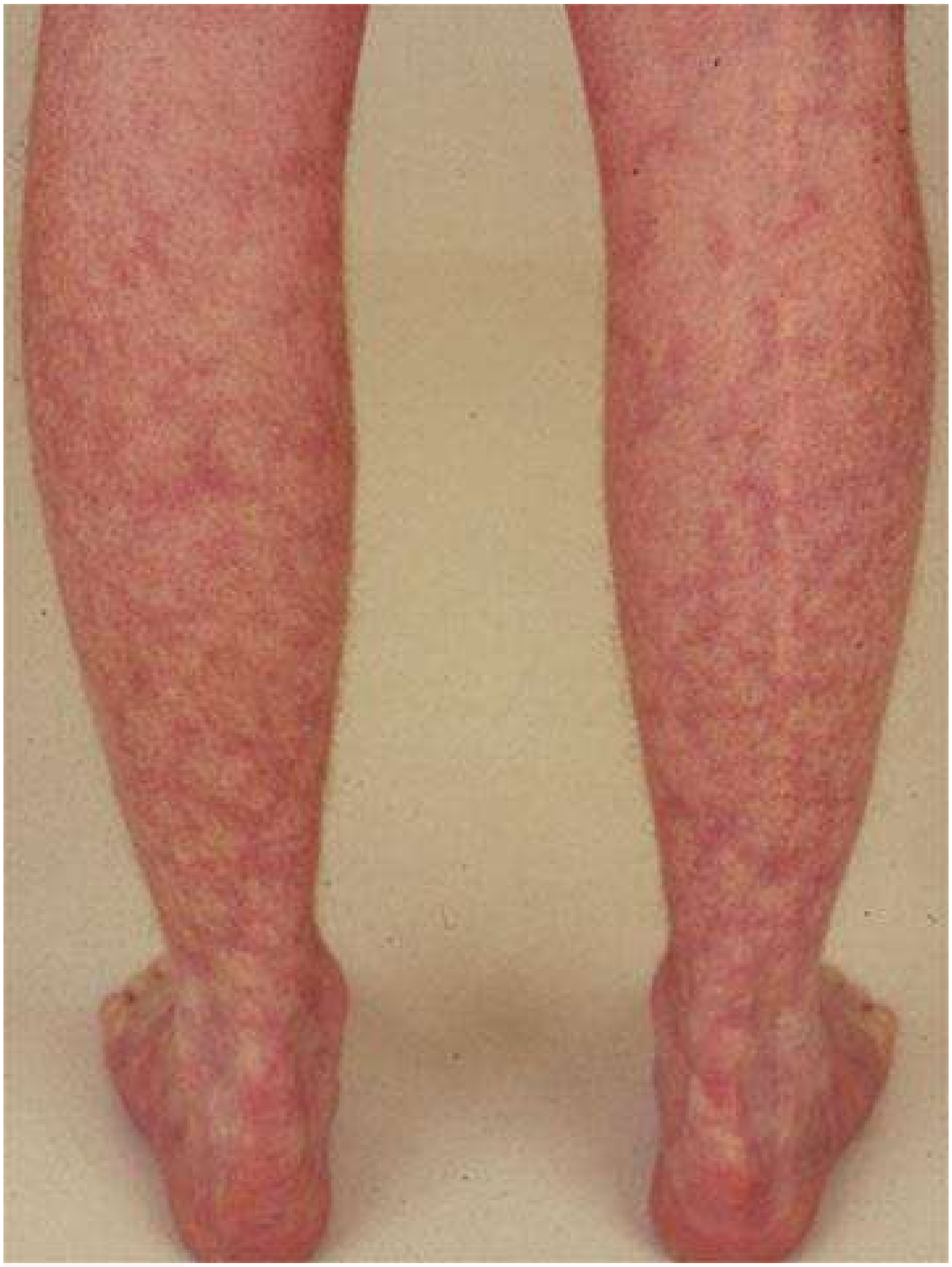
Treatment
- high-dose prednisolone - there should be a dramatic response, if not the diagnosis should be reconsidered
- urgent ophthalmology review. Patients with visual symptoms should be seen the same-day by an ophthalmologist. Visual damage is often irreversible

# POLYARTERITIS NODOSA

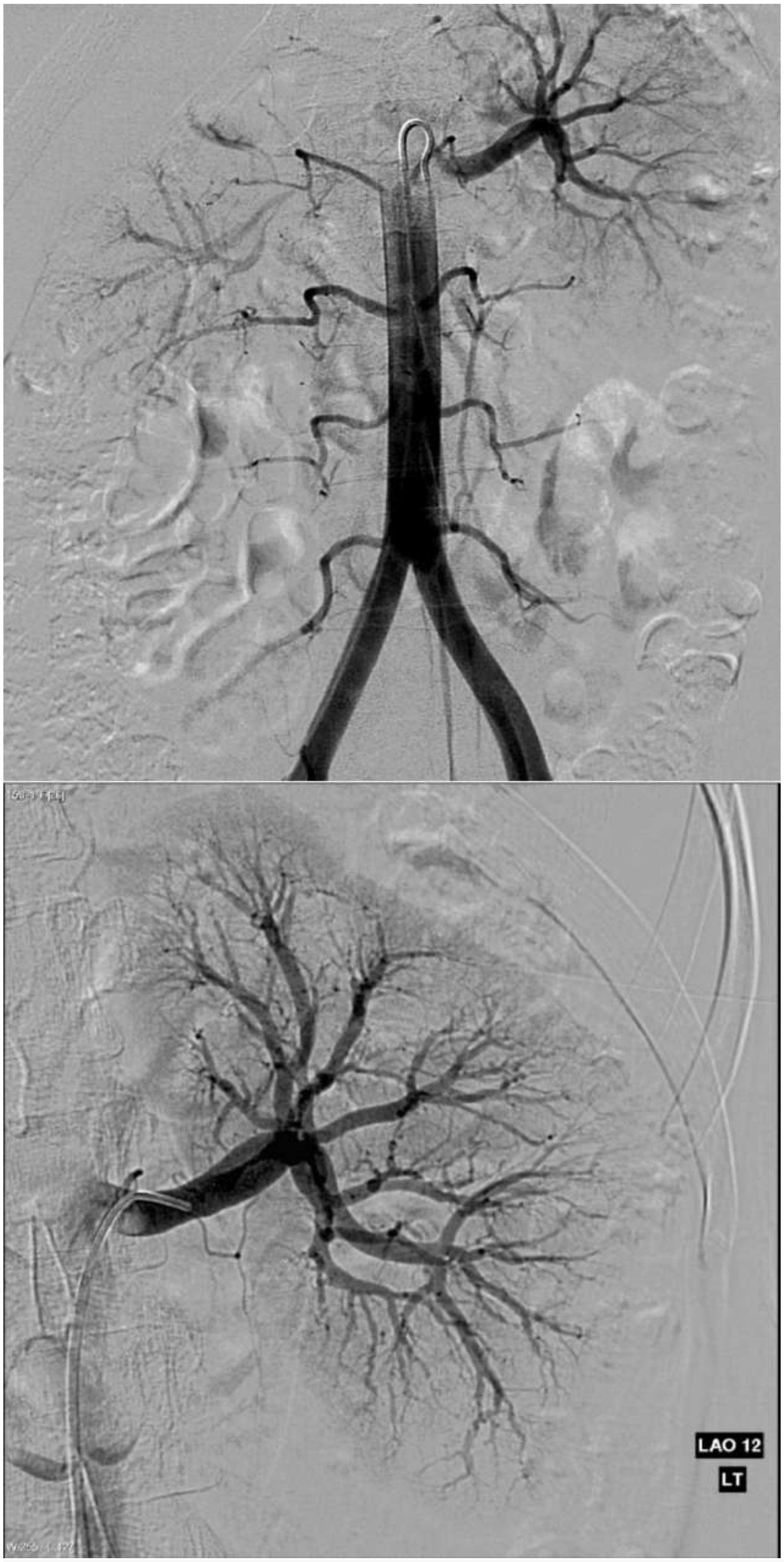
Polyarteritis nodosa (PAN) is a vasculitis affecting medium-sized arteries with necrotizing inflammation leading to aneurysm formation. PAN is more common in middle-aged men and is associated with hepatitis B infection.

Features
- fever, malaise, arthralgia
- weight loss
- hypertension
- mononeuritis multiplex, sensorimotor polyneuropathy
- testicular pain

- livedo reticularis
- haematuria, renal failure
- perinuclear-antineutrophil cytoplasmic antibodies (ANCA) are found in around 20% of patients with 'classic' PAN
- hepatitis B serology positive in 30% of patients



Livedo reticularis



Angiogram from a patient with polyarteritis nodosa. Both kidneys demonstrate beading and numerous microaneurysms affecting the intrarenal vessels. Similar changes are seen affecting the intrahepatic vessels with a few small microaneurysms noted. The proximal branches of the SMA appears normal; however there are no normal straight arteries from the jejunal arteries and lack of normal anastomotic arcades and loops. This is associated with multiple microaneurysms.

## BEHCET'S SYNDROME

Behcet's syndrome is a complex multisystem disorder associated with presumed autoimmune-mediated inflammation of the arteries and veins. The precise aetiology has yet to be elucidated however. The classic triad of symptoms are oral ulcers, genital ulcers and anterior uveitis

Epidemiology
- more common in the eastern Mediterranean (e.g. Turkey)
- more common in men (complicated gender distribution which varies according to country. Overall, Behcet's is considered to be more common and more severe in men)
- tends to affect young adults (e.g. 20 - 40 years old)
- associated with HLA B51
- around 30% of patients have a positive family history

Features
- classically: 1) oral ulcers 2) genital ulcers 3) anterior uveitis
- thrombophlebitis and deep vein thrombosis
- arthritis
- neurological involvement (e.g. aseptic meningitis)
- GI: abdo pain, diarrhoea, colitis
- erythema nodosum

Diagnosis
- no definitive test
- diagnosis based on clinical findings
- positive pathergy test is suggestive (puncture site following needle prick becomes inflamed with small pustule forming)

*more specifically HLA B51, a split antigen of HLA B5

# ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome is an acquired disorder characterised by a predisposition to both venous and arterial thromboses, recurrent fetal loss and thrombocytopenia. It may occur as a primary disorder or secondary to other conditions, most commonly systemic lupus erythematosus (SLE)

A key point for the exam is to appreciate that antiphospholipid syndrome causes a paradoxical rise in the APTT. This is due to an ex-vivo reaction of the lupus anticoagulant autoantibodies with phospholipids involved in the coagulation cascade

Features
- venous/arterial thrombosis
- recurrent fetal loss

- livedo reticularis
- thrombocytopenia
- prolonged APTT
- other features: pre-eclampsia, pulmonary hypertension

Associations other than SLE

- other autoimmune disorders
- lymphoproliferative disorders
- phenothiazines (rare)

Management - based on BCSH guidelines

- initial venous thromboembolic events: evidence currently supports use of warfarin with a target INR of 2-3 for 6 months
- recurrent venous thromboembolic events: lifelong warfarin; if occurred whilst taking warfarin then increase target INR to 3-4
- arterial thrombosis should be treated with lifelong warfarin with target INR 2-3

# GOUT: PREDISPOSING FACTORS

Gout is a form of microcrystal synovitis caused by the deposition of monosodium urate monohydrate in the synovium. It is caused by chronic hyperuricaemia (uric acid > 0.45 mmol/l)

Decreased excretion of uric acid

- drugs*: diuretics
- chronic kidney disease
- lead toxicity

Increased production of uric acid

- myeloproliferative/lymphoproliferative disorder
- cytotoxic drugs
- severe psoriasis

Lesch-Nyhan syndrome

- hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) deficiency
- x-linked recessive therefore only seen in boys
- features: gout, renal failure, neurological deficits, learning difficulties, self-mutilation

*aspirin in a dose of 75-150mg is not thought to have a significant effect on plasma urate levels - the British Society for Rheumatology recommend it should be continued if required for cardiovascular prophylaxis

# GOUT: DRUG CAUSES

Gout is a form of microcrystal synovitis caused by the deposition of monosodium urate monohydrate in the synovium. It is caused by chronic hyperuricaemia (uric acid > 0.45 mmol/l).

Drug causes

- diuretics: thiazides, furosemide
- ciclosporin
- alcohol
- cytotoxic agents
- pyrazinamide
- aspirin: it was previously thought that only high-dose aspirin could precipitate gout. However, a systematic review (see link) showed that low-dose (e.g. 75mg) also increases the risk of gout attacks. This obviously needs to be balanced against the cardiovascular benefits of aspirin and the study showed patients coprescribed allopurinol were not at an increased risk

# GOUT: FEATURES

Gout is a form of inflammatory arthritis. Patients typically have episodes lasting several days when their gout flares and are often symptom-free between episodes. The acute episodes typically develop maximal intensity with 12 hours/ The main features it presents with are:

- pain: this is often very significant
- swelling
- erythema

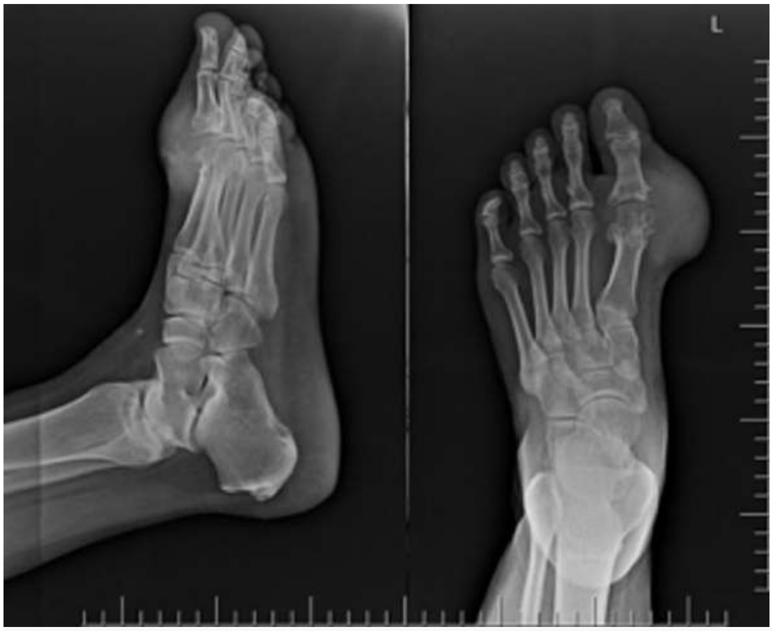
Around 70% of first presentations affect the 1st metatarsophalangeal (MTP) joint. Attacks of gout affecting this area were historically called podagra. Other commonly affected joints include:

- ankle
- wrist
- knee

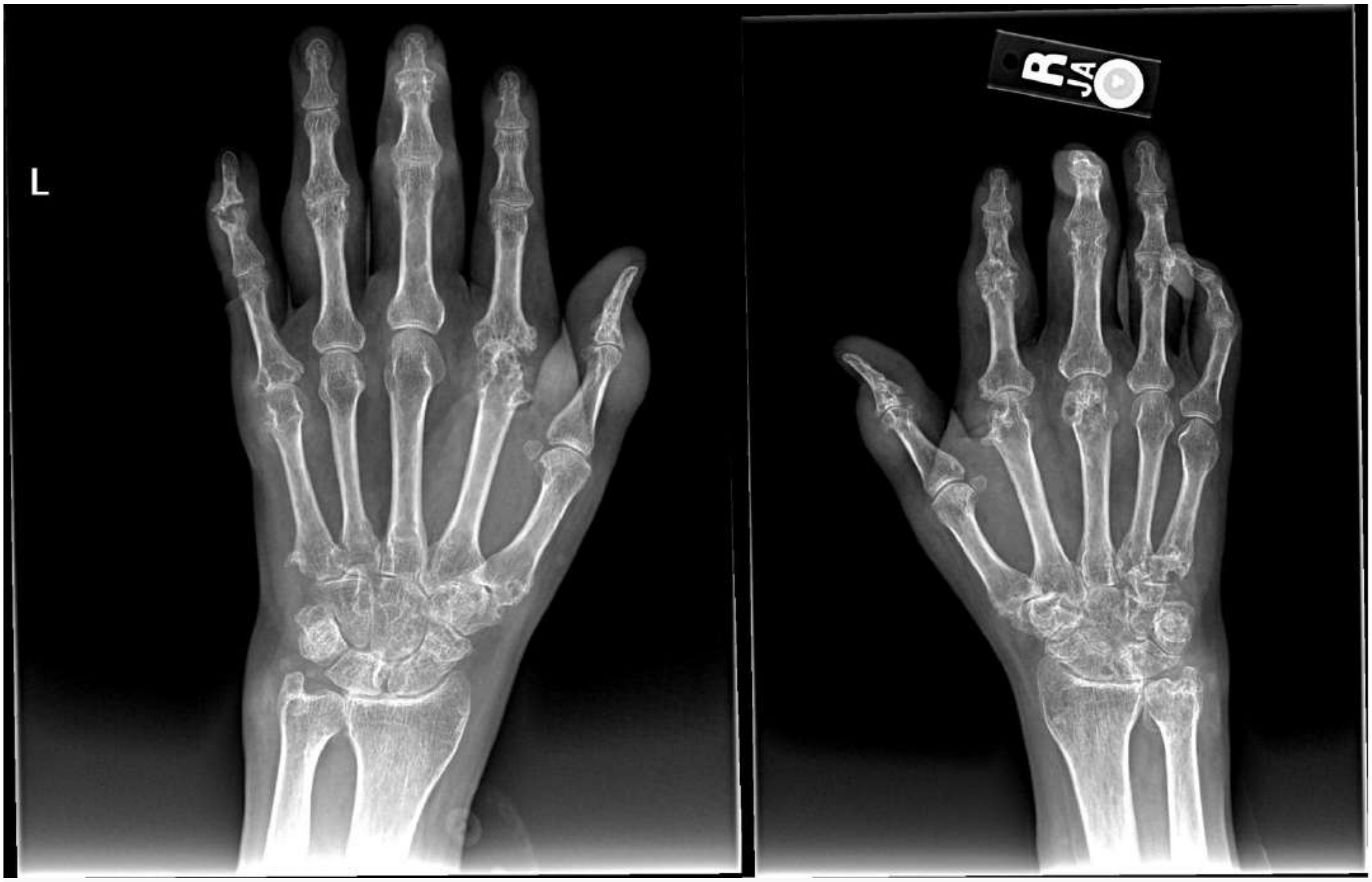
If untreated repeated acute episodes of gout can damage the joints resulting in a more chronic joint problem.

Radiological features of gout include:

- joint effusion is an early sign
- well-defined 'punched-out' erosions with sclerotic margins ina juxta-articular distribution, often with overhanging edges
- relative preservation of joint space until late disease
- eccentric erosions
- no periarticular osteopenia (in contrast to rheumatoid arthritis)
- soft tissue tophi may be seen



X ray of a patient with gout affecting his feet. It demonstrates juxta-articular erosive changes around the 1st MTP joint with overhanging edges and associated with a moderate soft tissue swelling. The joint space is maintained.



X-ray of a patient with gout affecting his hands. There are multiple periarticular erosions bilaterally with adjacent large soft tissue masses and relatively preserved joint spaces. In the right hand, these findings are most prominent at the 1st interphalangeal, 2nd-4th proximal interphalangeal, 1st-3rd metacarpophalangeal and carpometacarpal joints. In the left hand, the findings are most prominent at the ulnar styloid, scapholunate joint, first and fifth carpometacarpal joints, second and fifth metacarpophalangeal joints and 1st interphalangeal joint.

## GOUT: MANAGEMENT

Gout is a form of microcrystal synovitis caused by the deposition of monosodium urate monohydrate in the synovium. It is caused by chronic hyperuricaemia (uric acid > 450 µmol/l)

Acute management
- NSAIDs or colchicine are first-line
- the maximum dose of NSAID should be prescribed until 1-2 days after the symptoms have settled. Gastroprotection (e.g. a proton pump inhibitor) may also be indicated
- colchicine* has a slower onset of action. The main side-effect is diarrhoea
- oral steroids may be considered if NSAIDs and colchicine are contraindicated. A dose of prednisolone 15mg/day is usually used
- another option is intra-articular steroid injection
- if the patient is already taking allopurinol it should be continued

Indications for urate-lowering therapy (ULT)

- the British Society of Rheumatology Guidelines now advocate offering urate-lowering therapy to all patients after their **first attack of gout**
- ULT is particularly recommended if:
- → >= 2 attacks in 12 months
- → tophi
- → renal disease
- → uric acid renal stones
- → prophylaxis if on cytotoxics or diuretics

Urate-lowering therapy

- allopurinol is first-line
- it has traditionally been taught that urate-lowering therapy should not be started until 2 weeks after an acute attack, as starting too early may precipitate a further attack. The evidence base to support this however looks weak
- in 2017 the BSR updated their guidelines. They still support a delay in starting urate-lowering therapy because it is better for a patient to make long-term drug decisions whilst not in pain
- initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of < 300 µmol/l. Lower initial doses should be given if the patient has a reduced eGFR
- colchicine cover should be considered when starting allopurinol. NSAIDs can be used if colchicine cannot be tolerated. The BSR guidelines suggest this may need to be continued for 6 months
- the second-line agent when allopurinol is not tolerated or ineffective is febuxostat (also a xanthine oxidase inhibitor)
- in refractory cases other agents may be tried:
    - uricase (urate oxidase) is an enzyme that catalyzes the conversion of urate to the degradation product allantoin. It is present in certain mammals but not humans
    - in patients who have persistent symptomatic and severe gout despite the adequate use of urate-lowering therapy, pegloticase (polyethylene glycol modified mammalian uricase) can achieve rapid control of hyperuricemia. It is given as an infusion once every two weeks

Lifestyle modifications

- reduce alcohol intake and avoid during an acute attack
- lose weight if obese
- avoid food high in purines e.g. Liver, kidneys, seafood, oily fish (mackerel, sardines) and yeast products

Other points

- consideration should be given to stopping precipitating drugs (such as thiazides)
- losartan has a specific uricosuric action and may be particularly suitable for the many patients who have coexistent hypertension
- increased vitamin C intake (either supplements or through normal diet) may also decrease serum uric acid levels

*inhibits microtubule polymerization by binding to tubulin, interfering with mitosis. Also inhibits neutrophil motility and activity

# PSEUDOGOUT

Pseudogout is a form of microcrystal synovitis caused by the deposition of calcium pyrophosphate dihydrate crystals in the synovium.

Risk factors

- haemochromatosis
- hyperparathyroidism
- acromegaly
- low magnesium, low phosphate
- Wilson's disease

Features

- knee, wrist and shoulders most commonly affected
- joint aspiration: weakly-positively birefringent rhomboid-shaped crystals
- x-ray: chondrocalcinosis
- in the knee this can be seen as linear calcifications of the meniscus and articular cartilage

Management

- aspiration of joint fluid, to exclude septic arthritis
- NSAIDs or intra-articular, intra-muscular or oral steroids as for gout

# PSEUDOXANTHOMA ELASTICUM

Pseudoxanthoma elasticum is an inherited condition (usually autosomal recessive*) characterised by an abnormality in elastic fibres

Features
- retinal angioid streaks
- 'plucked chicken skin' appearance - small yellow papules on the neck, antecubital fossa and axillae
- cardiac: mitral valve prolapse, increased risk of ischaemic heart disease
- gastrointestinal haemorrhage

*there are reports of autosomal dominant inheritance in a minority of cases

# RELAPSING POLYCHONDRITIS

Relapsing polychondritis is a multi-systemic condition characterised by repeated episodes of inflammation and deterioration of cartilage. This most commonly affects the ears, however, can affect other parts of the body such as the nose and joints.

Key features:
- Ears: auricular chondritis, hearing loss, vertigo
- Nasal: nasal chondritis → saddle-nose deformity
- Respiratory tract: e.g. hoarseness, aphonia, wheezing, inspiratory stridor
- Ocular: episcleritis, scleritis, iritis, and keratoconjunctivitis sicca
- Joints: arthralgia
- Less commonly: cardiac valcular regurgitation, cranial nerve palsies, peripheral neuropathies, renal dysfunction

Diagnosis:
- Various scoring systems based on clinical, pathological, and radiological criteria

Treatment
- Induce remission: steroids
- Maintenance: azathioprine, methotrexate, cyclosporin, cyclophosphamide

# LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis is a rare condition associated with the abnormal proliferation of histiocytes. It typically presents in childhood with bony lesions.

Features

- bone pain, typically in the skull or proximal femur
- cutaneous nodules
- recurrent otitis media/mastoiditis
- tennis racket-shaped Birbeck granules on electromicroscopy

# FAMILIAL MEDITERRANEAN FEVER

Familial Mediterranean Fever (FMF, also known as recurrent polyserositis) is an autosomal recessive disorder which typically presents by the second decade. It is more common in people of Turkish, Armenian and Arabic descent

Features - attacks typically last 1-3 days

- pyrexia
- abdominal pain (due to peritonitis)
- pleurisy
- pericarditis
- arthritis
- erysipeloid rash on lower limbs

Management
colchicine may help

# MCARDLE'S DISEASE

Overview

- autosomal recessive type V glycogen storage disease
- caused by myophosphorylase deficiency
- this causes decreased muscle glycogenolysis

Features

- muscle pain and stiffness following exercise
- muscle cramps
- myoglobinuria
- low lactate levels during exercise

# STILL'S DISEASE IN ADULTS

Epidemiology

- has a bimodal age distribution - 15-25 yrs and 35-46 yrs

Features

- arthralgia
- elevated serum ferritin
- rash: salmon-pink, maculopapular
- pyrexia
  - typically rises in the late afternoon/early evening in a daily pattern and accompanies a worsening of joint symptoms and rash
- lymphadenopathy
- rheumatoid factor (RF) and anti-nuclear antibody (ANA) negative

The diagnosis of Still's disease in adults can be challenging. The Yamaguchi criteria is the most widely used criteria and has a sensitivity of 93.5%.

Management

- NSAIDs
  - should be used first-line to manage fever, joint pain and serositis
  - they should be trialled for at least a week before steroids are added.
- steroids
  - may control symptoms but won't improve prognosis
- if symptoms persist, the use of methotrexate, IL-1 or anti-TNF therapy can be considered

# PASSMEDICINE NOTES DERMATOLOGY

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# PRURITUS

The table below lists the main characteristics of the most important causes of pruritus

| Condition | Notes |
|---|---|
| **Liver disease** | History of alcohol excess<br>Stigmata of chronic liver disease: spider naevi, bruising, palmar erythema, gynaecomastia etc<br>Evidence of decompensation: ascites, jaundice, encephalopathy |
| **Iron deficiency anaemia** | Pallor<br>Other signs: koilonychia, atrophic glossitis, post-cricoid webs, angular stomatitis |
| **Polycythaemia** | Pruritus particularly after warm bath<br>'Ruddy complexion'<br>Gout<br>Peptic ulcer disease |
| **Chronic kidney disease** | Lethargy & pallor<br>Oedema & weight gain<br>Hypertension |
| **Lymphoma** | Night sweats<br>Lymphadenopathy<br>Splenomegaly, hepatomegaly<br>Fatigue |

Other causes:

- hyper- and hypothyroidism
- diabetes
- pregnancy
- 'senile' pruritus
- urticaria
- skin disorders: eczema, scabies, psoriasis, pityriasis rosea

# KOEBNER PHENOMENON

The Koebner phenomenon describes skin lesions which appear at the site of injury. It is seen in:
- psoriasis
- vitiligo
- warts
- lichen planus
- lichen sclerosus
- molluscum contagiosum

# MOLLUSCUM CONTAGIOSUM

Molluscum contagiosum is a common skin infection caused by molluscum contagiosum virus (MCV), a member of the Poxviridae family. Transmission occurs directly by close personal contact, or indirectly via fomites (contaminated surfaces) such as shared towels and flannels. The majority of cases occur in children (often in children with atopic eczema), with the maximum incidence in preschool children aged 1-4 years.

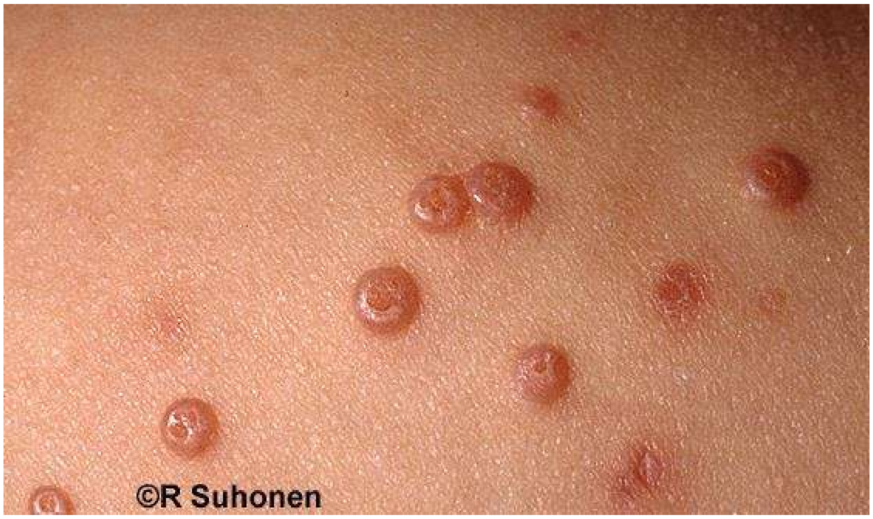
Typically, molluscum contagiosum presents with characteristic pinkish or pearly white papules with a central umbilication, which are up to 5 mm in diameter. Lesions appear in clusters in areas anywhere on the body (except the palms of the hands and the soles of the feet). In children, lesions are commonly seen on the trunk and in flexures, but anogenital lesions may also occur. In adults, sexual contact may lead to lesions developing on the genitalia, pubis, thighs, and lower abdomen. Rarely, lesions can occur on the oral mucosa and on the eyelids.

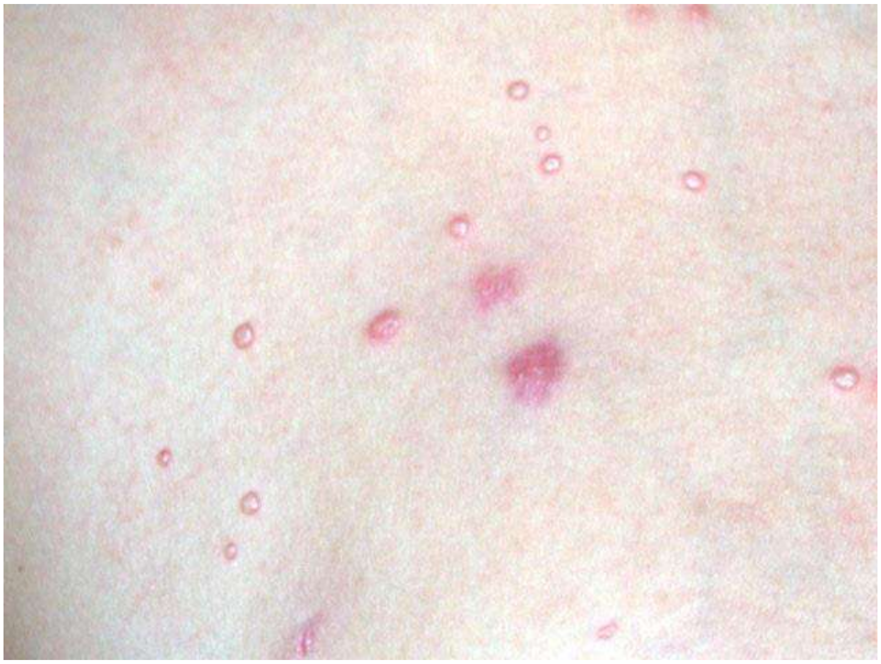
Self care advice:
- Reassure people that molluscum contagiosum is a self-limiting condition.
- Spontaneous resolution usually occurs within 18 months
- Explain that lesions are contagious, and it is sensible to avoid sharing towels, clothing, and baths with uninfected people (e.g. siblings)
- Encourage people not to scratch the lesions. If it is problematic, consider treatment to alleviate the itch
- Exclusion from school, gym, or swimming is not necessary

Treatment is not usually recommended. If lesions are troublesome or considered unsightly, use simple trauma or cryotherapy, depending on the parents' wishes and the child's age:
- Squeezing (with fingernails) or piercing (orange stick) lesions may be tried, following a bath. Treatment should be limited to a few lesions at one time
- Cryotherapy may be used in older children or adults, if the healthcare professional is experienced in the procedure

- Eczema or inflammation can develop around lesions prior to resolution. Treatment may be required if:
- → Itching is problematic; prescribe an emollient and a mild topical corticosteroid (e.g. hydrocortisone 1%)
- → The skin looks infected (e.g. oedema, crusting); prescribe a topical antibiotic (e.g. fusidic acid 2%)

Referral may be necessary in some circumstances:
- For people who are HIV-positive with extensive lesions urgent referral to a HIV specialist
- For people with eyelid-margin or ocular lesions and associated red eye urgent referral to an ophthalmologist
- Adults with anogenital lesions should be referred to genito-urinary medicine, for screening for other sexually transmitted infections





# VITILIGO

Vitiligo is an autoimmune condition which results in the loss of melanocytes and consequent depigmentation of the skin. It is thought to affect around 1% of the population and symptoms typically develop by the age of 20-30 years.

Features

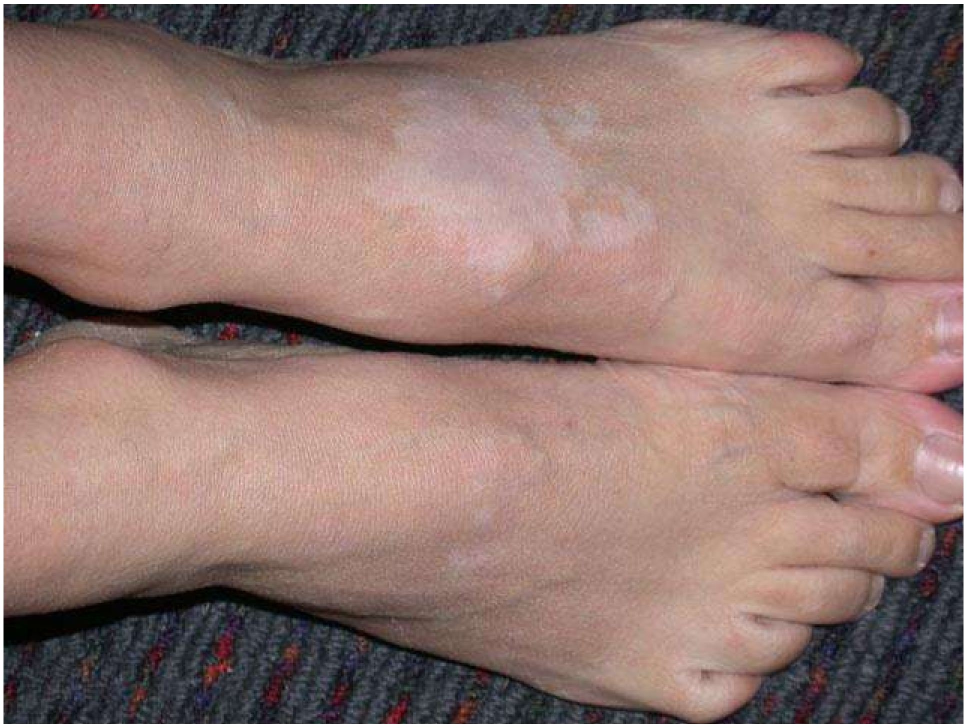
- well-demarcated patches of depigmented skin
- the peripheries tend to be most affected
- trauma may precipitate new lesions (Koebner phenomenon)

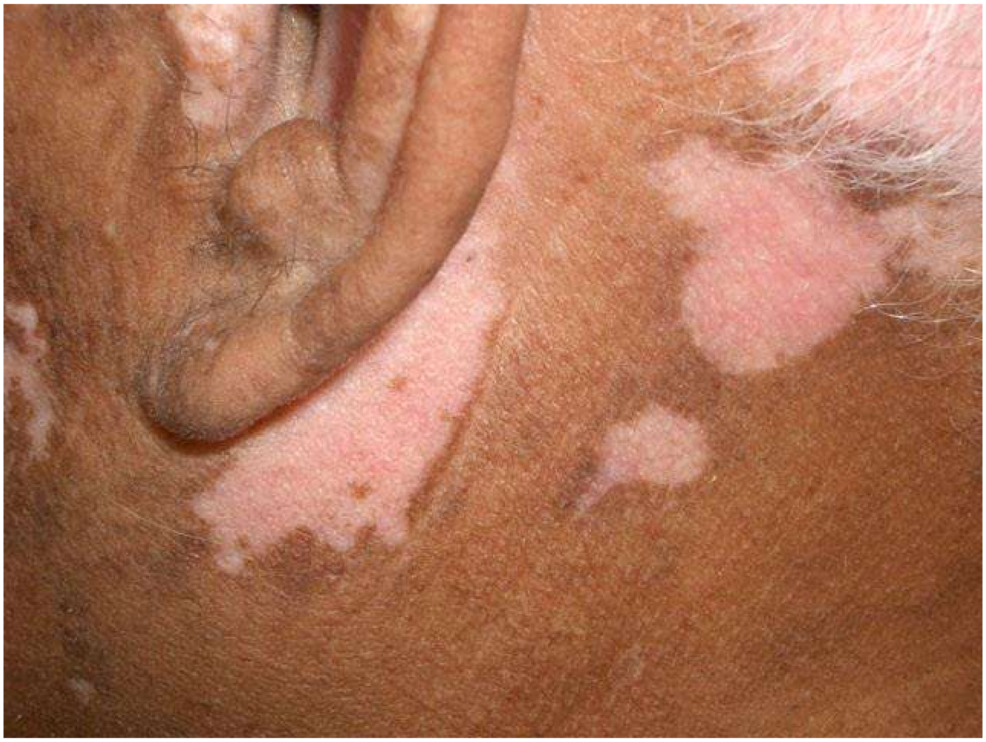
Associated conditions

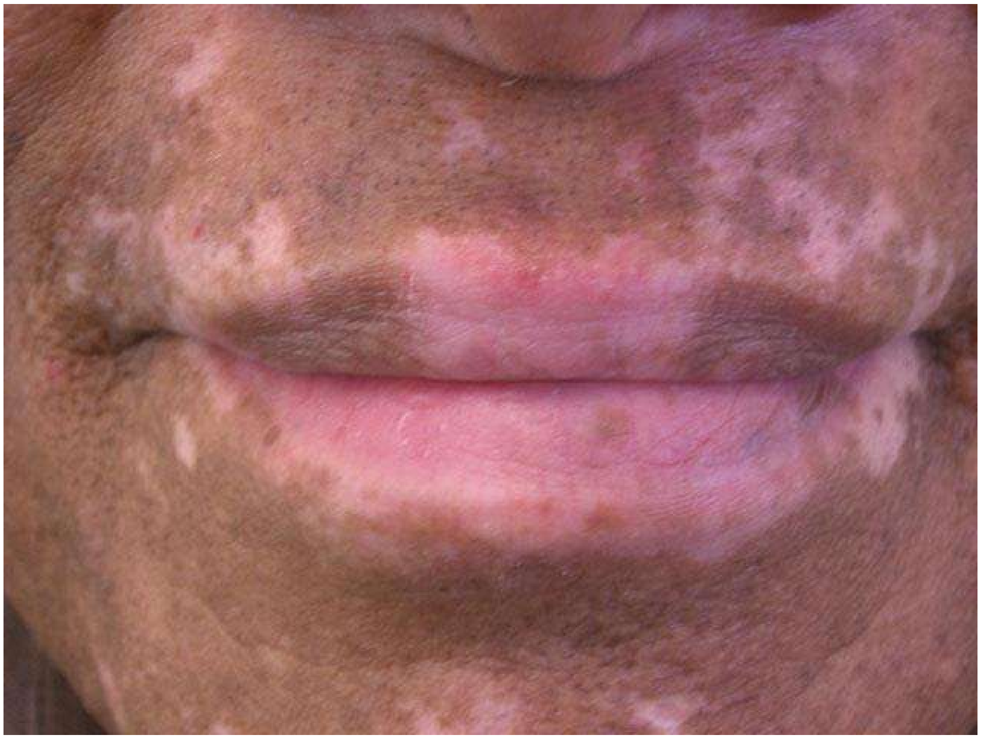
- type 1 diabetes mellitus
- Addison's disease
- autoimmune thyroid disorders
- pernicious anaemia
- alopecia areata

Management

- sunblock for affected areas of skin
- camouflage make-up
- topical corticosteroids may reverse the changes if applied early
- there may also be a role for topical tacrolimus and phototherapy, although caution needs to be exercised with light-skinned patients







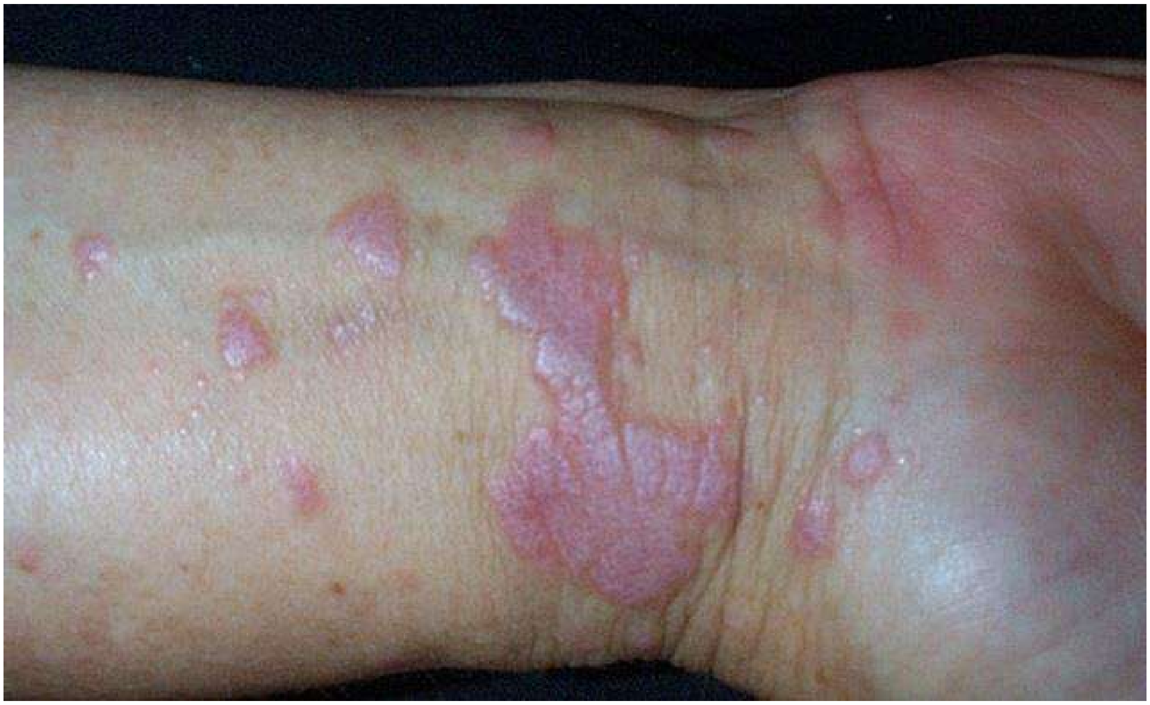
# LICHEN PLANUS

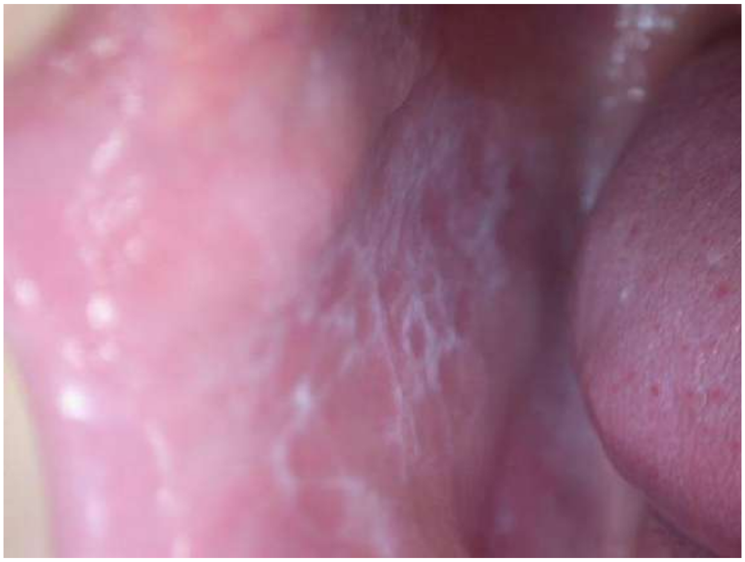
Lichen planus is a skin disorder of unknown aetiology, most probably being immune-mediated.

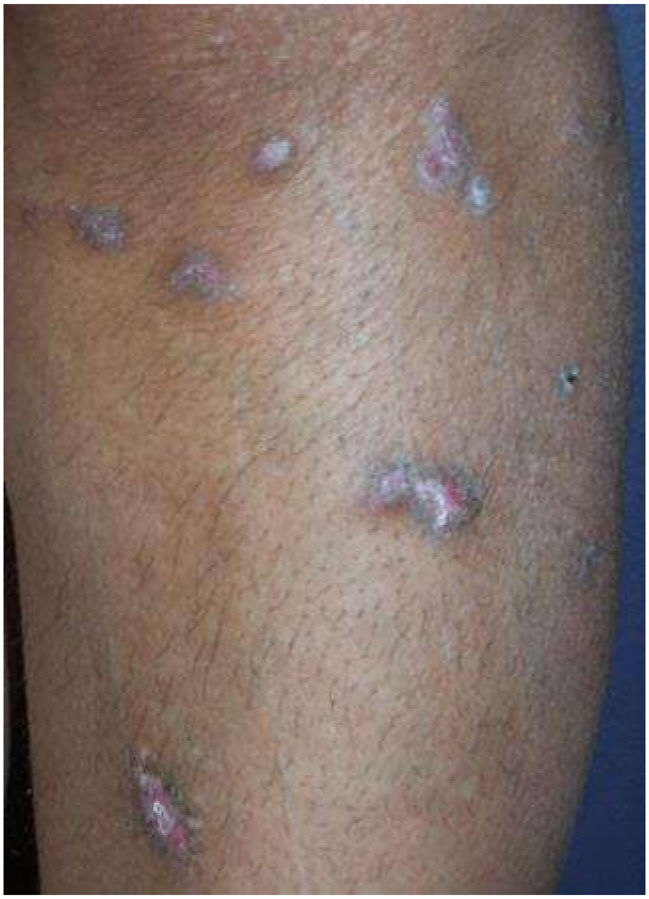
Features
- itchy, papular rash most common on the palms, soles, genitalia and flexor surfaces of arms
- rash often polygonal in shape, with a 'white-lines' pattern on the surface (Wickham's striae)
- Koebner phenomenon may be seen (new skin lesions appearing at the site of trauma)
- oral involvement in around 50% of patients: typically a white-lace pattern on the buccal mucosa
- nails: thinning of nail plate, longitudinal ridging

Lichenoid drug eruptions - causes:
- gold
- quinine
- thiazides

Management
- potent topical steroids are the mainstay of treatment
- benzydamine mouthwash or spray is recommended for oral lichen planus
- extensive lichen planus may require oral steroids or immunosuppression







## LICHEN SCLEROSUS

Lichen sclerosus was previously termed lichen sclerosus et atrophicus. It is an inflammatory condition which usually affects the genitalia and is more common in elderly females. Lichen sclerosus leads to atrophy of the epidermis with white plaques forming

Features
- itch is prominent

The diagnosis is usually made on clinical grounds but a biopsy may be performed if atypical features are present*

Management
- topical steroids and emollients

Follow-up:
- increased risk of vulval cancer

*the RCOG advise the following

*Skin biopsy is not necessary when a diagnosis can be made on clinical examination. Biopsy is required if the woman fails to respond to treatment or there is clinical suspicion of VIN or cancer.*

and the British Association of Dermatologists state the following:

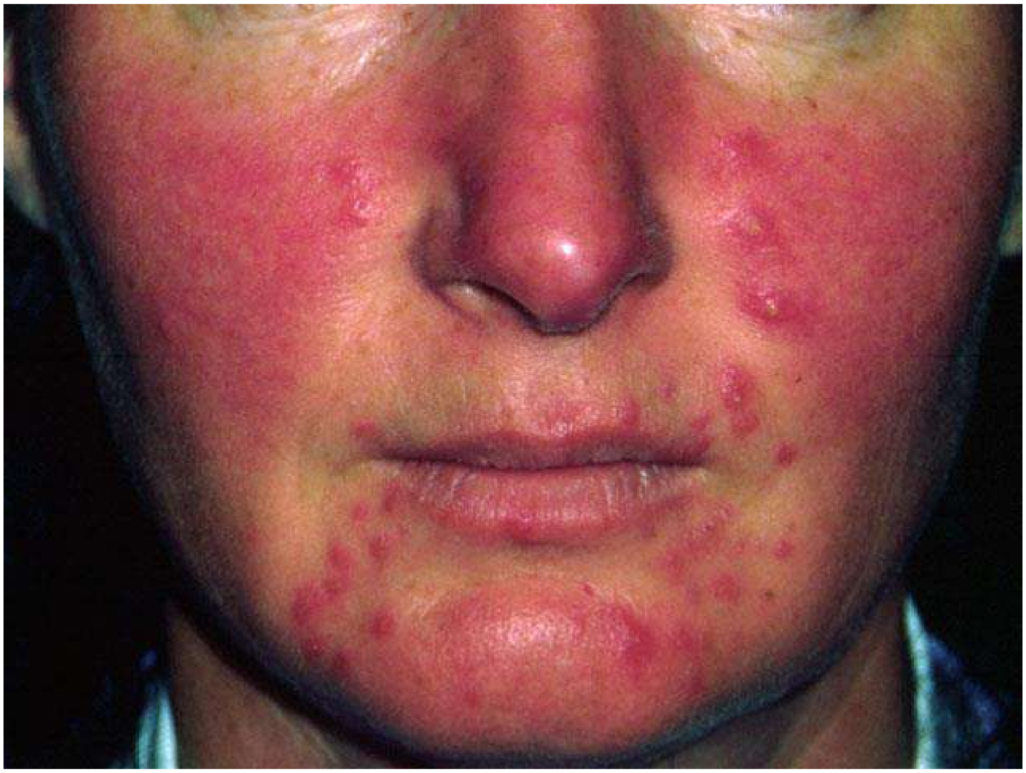
*A confirmatory biopsy, although ideal, is not always practical, particularly in children. It is not always essential when the clinical features are typical. However, histological examination is advisable if there are atypical features or diagnostic uncertainty and is mandatory if there is any suspicion of neoplastic*
*change. Patients under routine follow-up will need a biopsy if:*
*(i) there is a suspicion of neoplastic change, i.e. a persistent area of hyperkeratosis, erosion or erythema, or new warty or papular lesions;*
*(ii) the disease fails to respond to adequate treatment;*
*(iii) there is extragenital LS, with features suggesting an overlap with morphoea;*
*(iv) there are pigmented areas, in order to exclude an abnormal melanocytic proliferation;*
*and*
*(v) second-line therapy is to be used.*

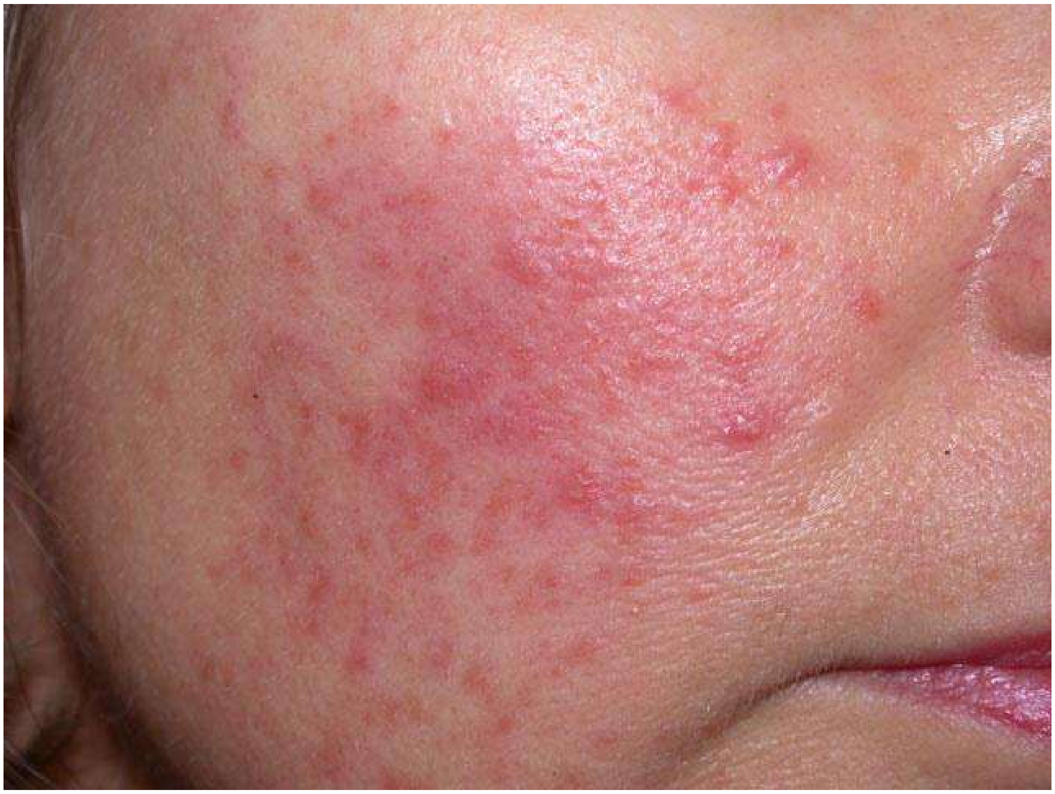
# ACNE ROSACEA

Acne rosacea is a chronic skin disease of unknown aetiology.

Features
- typically affects nose, cheeks and forehead
- flushing is often first symptom
- telangiectasia are common
- later develops into persistent erythema with papules and pustules
- rhinophyma
- ocular involvement: blepharitis
- sunlight may exacerbate symptoms/

Management
- topical metronidazole may be used for mild symptoms (i.e. Limited number of papules and pustules, no plaques)
- topical brimonidine gel may be considered for patients with predominant flushing but limited telangiectasia
- more severe disease is treated with systemic antibiotics e.g. Oxytetracycline
- recommend daily application of a high-factor sunscreen
- camouflage creams may help conceal redness
- laser therapy may be appropriate for patients with prominent telangiectasia
- patients with a rhinophyma should be referred to dermatology





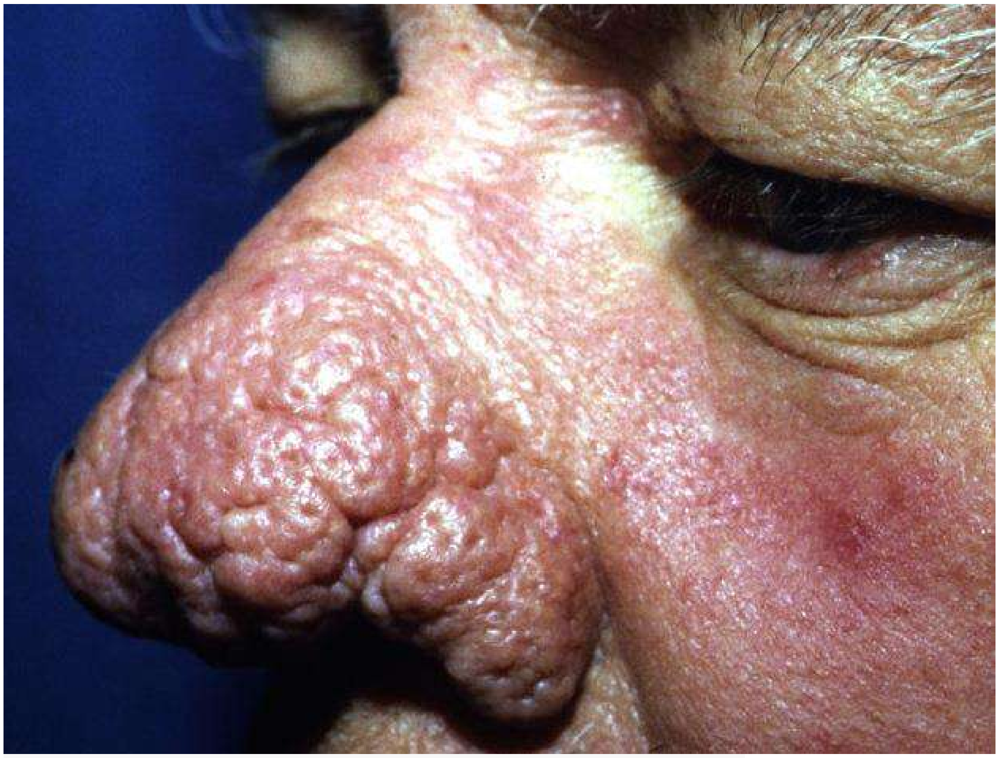


Image showing a rhinophyma - a late complication of severe rosacea

# ACNE VULGARIS

Acne vulgaris is a common skin disorder which usually occurs in adolescence. It typically affects the face, neck and upper trunk and is characterised by the obstruction of the pilosebaceous follicle with keratin plugs which results in comedones, inflammation and pustules.

Epidemiology
- affects around 80-90% of teenagers, 60% of whom seek medical advice
- acne may also persist beyond adolescence, with 10-15% of females and 5% of males over 25 years old being affected

Pathophysiology is multifactorial
- follicular epidermal hyperproliferation resulting in the formation of a keratin plug. This in turn causes obstruction of the pilosebaceous follicle. Activity of sebaceous glands may be controlled by androgen, although levels are often normal in patients with acne
- colonisation by the anaerobic bacterium Propionibacterium acnes
- inflammation

# ACNE VULGARIS: MANAGEMENT

Acne vulgaris is a common skin disorder which usually occurs in adolescence. It typically affects the face, neck and upper trunk and is characterised by the obstruction of the pilosebaceous follicles with keratin plugs which results in comedones, inflammation and pustules.

Acne may be classified into mild, moderate or severe:
- mild: open and closed comedones with or without sparse inflammatory lesions
- moderate acne: widespread non-inflammatory lesions and numerous papules and pustules
- severe acne: extensive inflammatory lesions, which may include nodules, pitting, and scarring

A simple step-up management scheme often used in the treatment of acne is as follows:
- single topical therapy (topical retinoids, benzoyl peroxide)
- topical combination therapy (topical antibiotic, benzoyl peroxide, topical retinoid)
- oral antibiotics:
  - tetracyclines: lymecycline, oxytetracycline, doxycycline
  - tetracyclines should be avoided in pregnant or breastfeeding women and in children younger than 12 years of age
  - erythromycin may be used in pregnancy
  - minocycline is now considered less appropriate due to the possibility of irreversible pigmentation
  - a single oral antibiotic for acne vulgaris should be used for a maximum of three months
  - a topical retinoid (if not contraindicated) or benzoyl peroxide should always be co-prescribed with oral antibiotics to reduce the risk of antibiotic resistance developing. Topical and oral antibiotics should not be used in combination

  - Gram-negative folliculitis may occur as a complication of long-term antibiotic use - high-dose oral trimethoprim is effective if this occurs
- combined oral contraceptives (COCP) are an alternative to oral antibiotics in women
  - as with antibiotics, they should be used in combination with topical agents
  - Dianette (co-cyrindiol) is sometimes used as it has anti-androgen properties. However, it has an increased risk of venous thromboembolism compared to other COCPs, therefore it should generally be used second-line, only be given for 3 months and women should be appropriately counselled about the risks
- oral isotretinoin: only under specialist supervision
  - pregnancy is a contraindication to topical and oral retinoid treatment

There is no role for dietary modification in patients with acne.

## RETINOIDS

### Isotretinoin

Isotretinoin is an oral retinoid used in the treatment of severe acne. Two-thirds of patients have a long-term remission or cure following a course of oral isotretinoin.

Adverse effects

- teratogenicity: females should ideally be using two forms of contraception (e.g. Combined oral contraceptive pill and condoms)
- dry skin, eyes and lips/mouth: the most common side-effect of isotretinoin
- low mood*
- raised triglycerides
- hair thinning
- nose bleeds (caused by dryness of the nasal mucosa)
- intracranial hypertension: isotretinoin treatment should not be combined with tetracyclines for this reason
- photosensitivity

*whilst this is a controversial topic, depression and other psychiatric problems are listed in the BNF

# ALOPECIA

Alopecia may be divided into scarring (destruction of hair follicle) and non-scarring (preservation of hair follicle)

Scarring alopecia
- trauma, burns
- radiotherapy
- lichen planus
- discoid lupus
- tinea capitis*

Non-scarring alopecia
- male-pattern baldness
- drugs: cytotoxic drugs, carbimazole, heparin, oral contraceptive pill, colchicine
- nutritional: iron and zinc deficiency
- autoimmune: alopecia areata
- telogen effluvium
  - hair loss following stressful period e.g. surgery
- trichotillomania

*scarring may develop in untreated tinea capitis if a kerion develops

# ALOPECIA AREATA

Alopecia areata is a presumed autoimmune condition causing localised, well demarcated patches of hair loss. At the edge of the hair loss, there may be small, broken 'exclamation mark' hairs

Hair will regrow in 50% of patients by 1 year, and in 80-90% eventually. Careful explanation is therefore sufficient in many patients. Other treatment options include:
- topical or intralesional corticosteroids
- topical minoxidil
- phototherapy
- dithranol
- contact immunotherapy
- wigs

# HIRSUTISM AND HYPERTRICHOSIS

Hirsutism is often used to describe androgen-dependent hair growth in women, with hypertrichosis being used for androgen-independent hair growth

Polycystic ovarian syndrome is the most common causes of hirsutism. Other causes include:
- Cushing's syndrome
- congenital adrenal hyperplasia
- androgen therapy
- obesity: thought to be due to insulin resistance
- adrenal tumour
- androgen secreting ovarian tumour
- drugs: phenytoin, corticosteroids

Assessment of hirsutism
- Ferriman-Gallwey scoring system: 9 body areas are assigned a score of 0 - 4, a score > 15 is considered to indicate moderate or severe hirsutism

Management of hirsutism
- advise weight loss if overweight
- cosmetic techniques such as waxing/bleaching - not available on the NHS
- consider using combined oral contraceptive pills such as co-cyprindiol (Dianette) or ethinylestradiol and drospirenone (Yasmin). Co-cyprindiol should not be used long-term due to the increased risk of venous thromboembolism
- facial hirsutism: topical eflornithine - contraindicated in pregnancy and breast-feeding

Causes of hypertrichosis
- drugs: minoxidil, ciclosporin, diazoxide
- congenital hypertrichosis lanuginosa, congenital hypertrichosis terminalis
- porphyria cutanea tarda
- anorexia nervosa

# HYPERHIDROSIS

Hyperhidrosis describes the excessive production of sweat.

Management options include
- topical aluminium chloride preparations are first-line. Main side effect is skin irritation
- iontophoresis: particularly useful for patients with palmar, plantar and axillary hyperhidrosis
- botulinum toxin: currently licensed for axillary symptoms
- surgery: e.g. Endoscopic transthoracic sympathectomy. Patients should be made aware of the risk of compensatory sweating

# IMPETIGO

Impetigo is a superficial bacterial skin infection usually caused by either Staphylcoccus aureus or Streptococcus pyogenes. It can be a primary infection or a complication of an existing skin condition such as eczema (in this case), scabies or insect bites. Impetigo is common in children, particularly during warm weather.

The infection can develop anywhere on the body but lesions tend to occur on the face, flexures and limbs not covered by clothing.

Spread is by direct contact with discharges from the scabs of an infected person. The bacteria invade the skin through minor abrasions and then spread to other sites by scratching. Infection is spread mainly by the hands, but indirect spread via toys, clothing, equipment and the environment may occur. The incubation period is between 4 to 10 days.

Features

- 'golden', crusted skin lesions typically found around the mouth
- very contagious

**Management**

Limited, localised disease

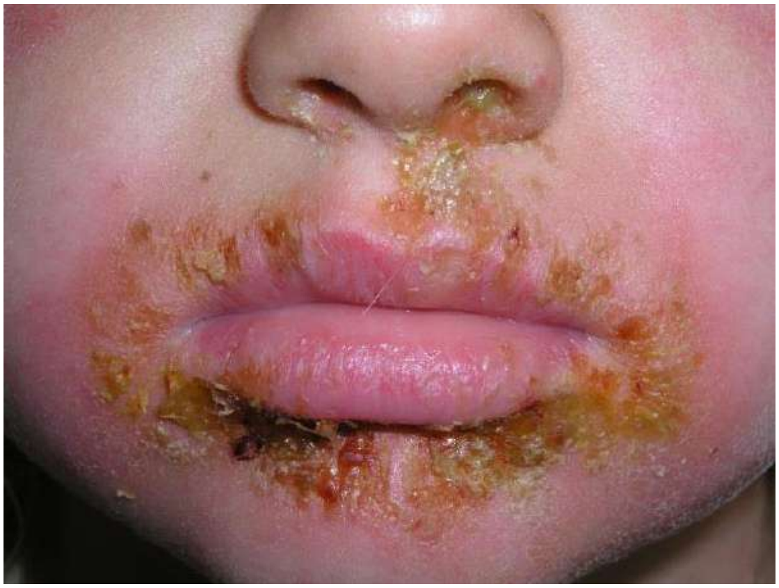
- NICE Clinical Knowledge Summaries now recommend **hydrogen peroxide 1% cream** for 'people who are not systemically unwell or at a high risk of complications'
    - the change was announced in 2020 by NICE and Public Health England and seems aimed at cutting antibiotic resistance
    - the evidence base shows it is just as effective at treating non-bullous impetigo as a topical antibiotic
- topical antibiotic creams:
    - topical fusidic acid
    - topical mupirocin should be used if fusidic acid resistance is suspected
    - MRSA is not susceptible to either fusidic acid or retapamulin. Topical mupirocin should, therefore, be used in this situation

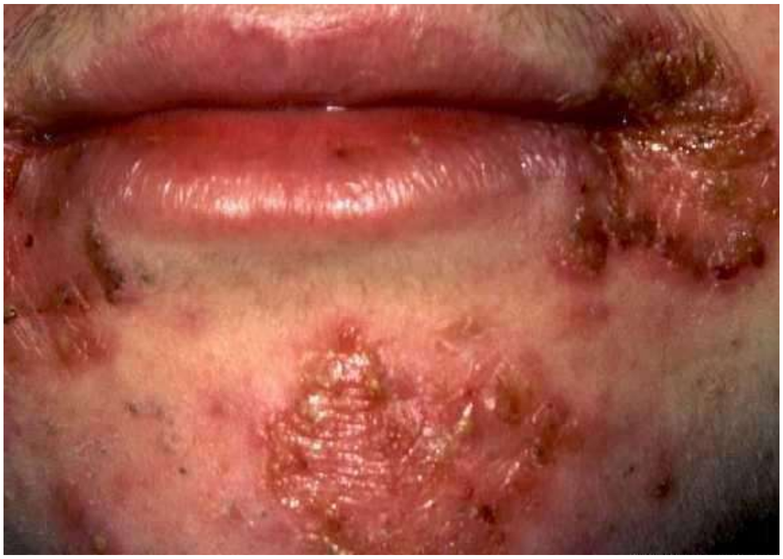
Extensive disease

- oral flucloxacillin
- oral erythromycin if penicillin-allergic

School exclusion

- children should be excluded from school until the lesions are crusted and healed or 48 hours after commencing antibiotic treatment





# KELOID SCARS

Keloid scars are tumour-like lesions that arise from the connective tissue of a scar and extend beyond the dimensions of the original wound

Predisposing factors

- ethnicity: more common in people with dark skin
- occur more commonly in young adults, rare in the elderly
- common sites (in order of decreasing frequency): sternum, shoulder, neck, face, extensor surface of limbs, trunk

Keloid scars are less likely if incisions are made along relaxed skin tension lines*

Treatment

- early keloids may be treated with intra-lesional steroids e.g. triamcinolone
- excision is sometimes required

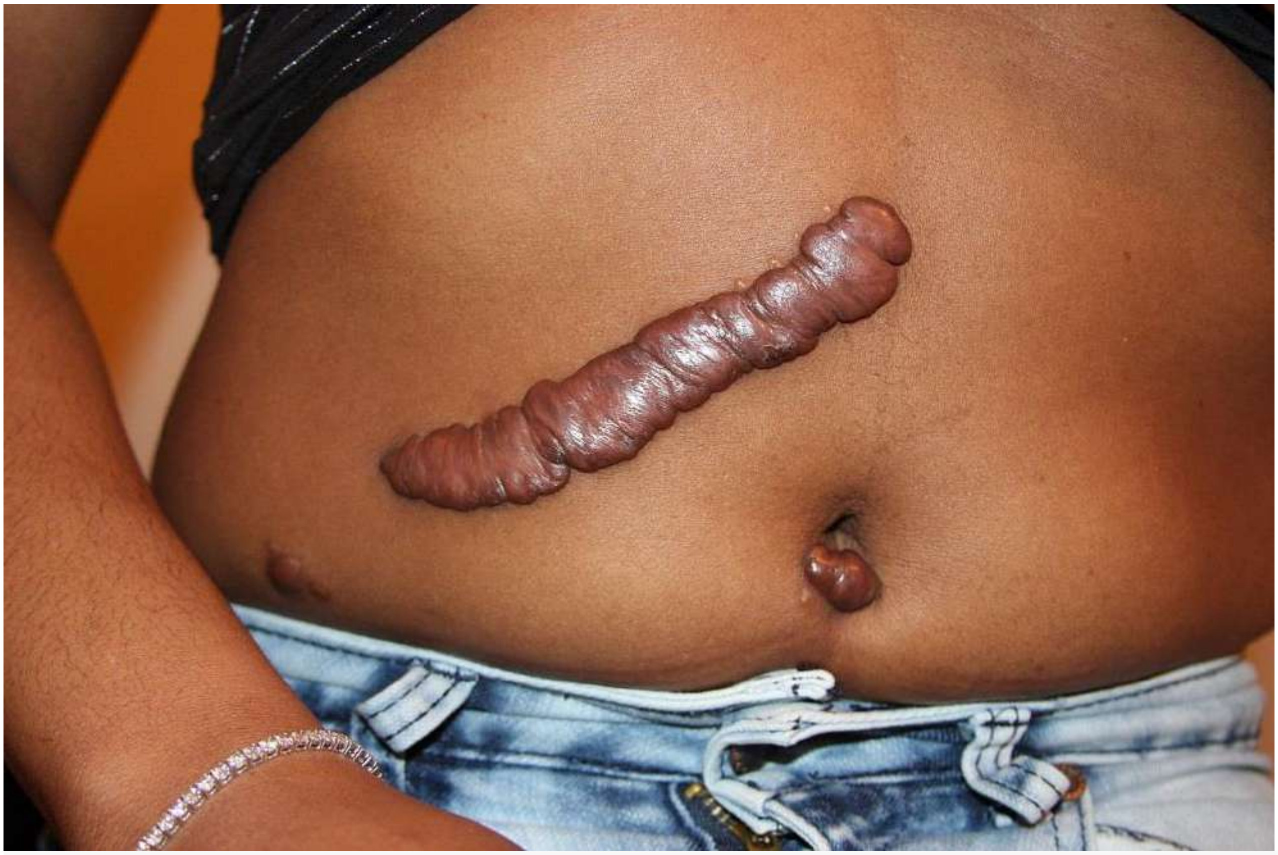


Image showing a keloid scar at the site of abdominal surgery. Note the lesions below the umbilicus and also in the right iliac fossa. This was possibly a laparoscopic procedure that was 'converted' to a laparotomy.

*Langer lines were historically used to determine the optimal incision line. They were based on procedures done on cadavers but have been shown to produce worse cosmetic results than when following skin tension lines

# PSORIASIS

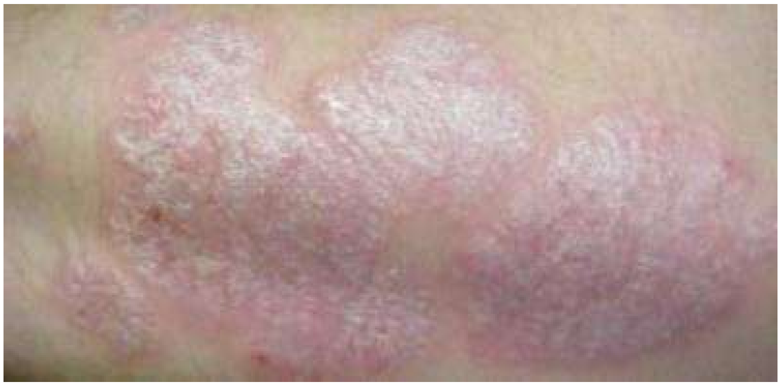
Psoriasis is a common (prevalence around 2%) and chronic skin disorder. It generally presents with red, scaly patches on the skin although it is now recognised that patients with psoriasis are at increased risk of arthritis and cardiovascular disease.

Pathophysiology

- multifactorial and not yet fully understood
- genetic: associated HLA-B13, -B17, and -Cw6. Strong concordance (70%) in identical twins
- immunological: abnormal T cell activity stimulates keratinocyte proliferation. There is increasing evidence this may be mediated by a novel group of T helper cells producing IL-17, designated Th17. These cells seem to be a third T-effector cell subset in addition to Th1 and Th2
- environmental: it is recognised that psoriasis may be worsened (e.g. Skin trauma, stress), triggered (e.g. Streptococcal infection) or improved (e.g. Sunlight) by environmental factors

Recognised subtypes of psoriasis

- plaque psoriasis: the most common sub-type resulting in the typical well demarcated red, scaly patches affecting the extensor surfaces, sacrum and scalp
- flexural psoriasis: in contrast to plaque psoriasis the skin is smooth
- guttate psoriasis: transient psoriatic rash frequently triggered by a streptococcal infection. Multiple red, teardrop lesions appear on the body
- pustular psoriasis: commonly occurs on the palms and soles



Other features

- nail signs: pitting, onycholysis
- arthritis

Complications

- psoriatic arthropathy (around 10%)
- increased incidence of metabolic syndrome
- increased incidence of cardiovascular disease
- increased incidence of venous thromboembolism
- psychological distress

## PSORIASIS: EXACERBATING FACTORS

The following factors may exacerbate psoriasis:

- trauma
- alcohol
- drugs: beta blockers, lithium, antimalarials (chloroquine and hydroxychloroquine), NSAIDs and ACE inhibitors, infliximab
- withdrawal of systemic steroids

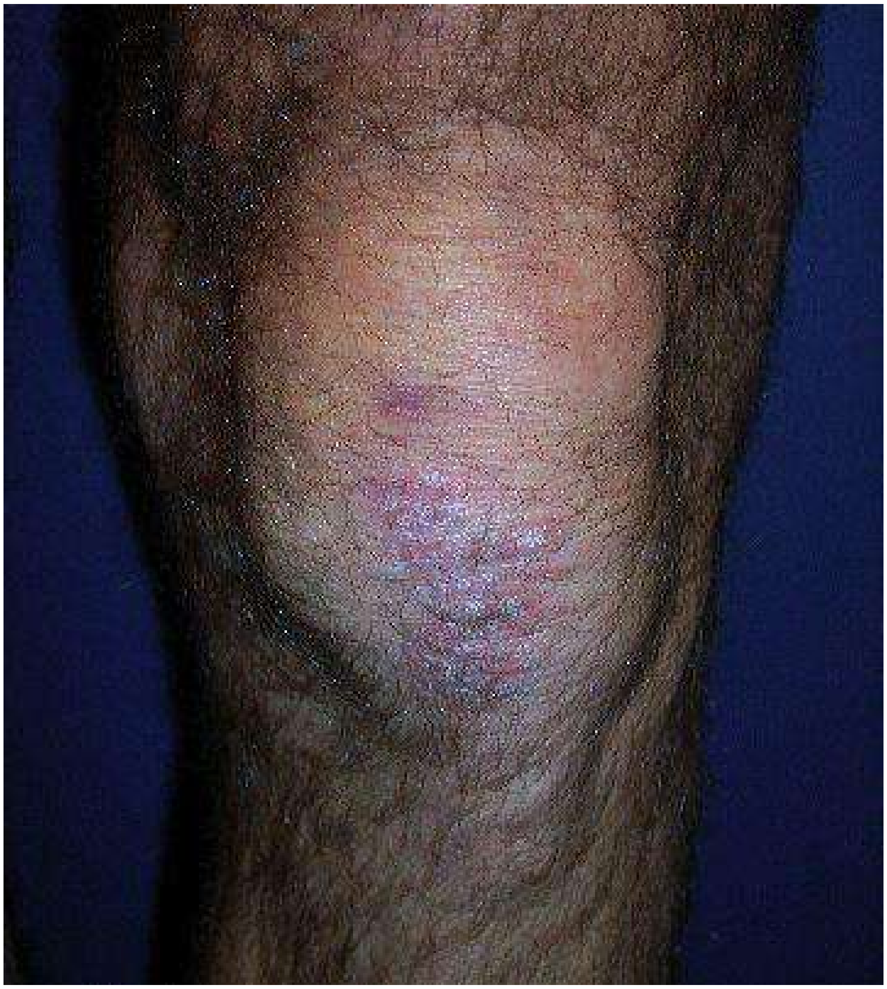
Streptococcal infection may trigger guttate psoriasis.

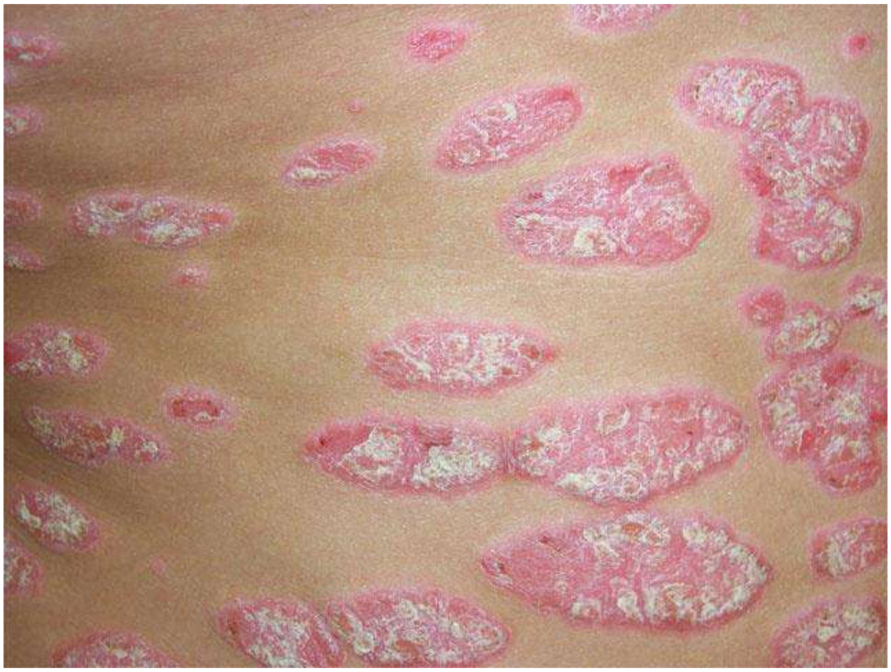
## PSORIASIS: MANAGEMENT

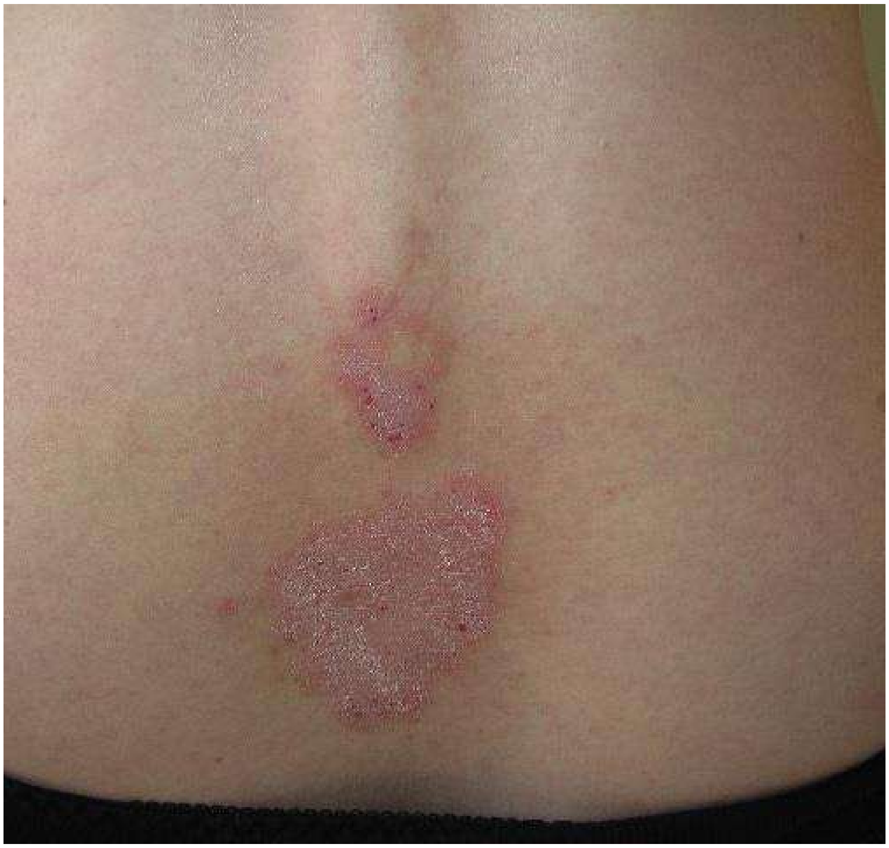
NICE released guidelines in 2012 on the management of psoriasis and psoriatic arthropathy. Please see the link for more details.

Management of chronic plaque psoriasis

- regular emollients may help to reduce scale loss and reduce pruritus
- first-line: NICE recommend a potent corticosteroid applied once daily plus vitamin D analogue applied once daily (applied separately, one in the morning and the other in the evening) for up to 4 weeks as initial treatment
- second-line: if no improvement after 8 weeks then offer a vitamin D analogue twice daily
- third-line: if no improvement after 8-12 weeks then offer either: a potent corticosteroid applied twice daily for up to 4 weeks or a coal tar preparation applied once or twice daily
- short-acting dithranol can also be used





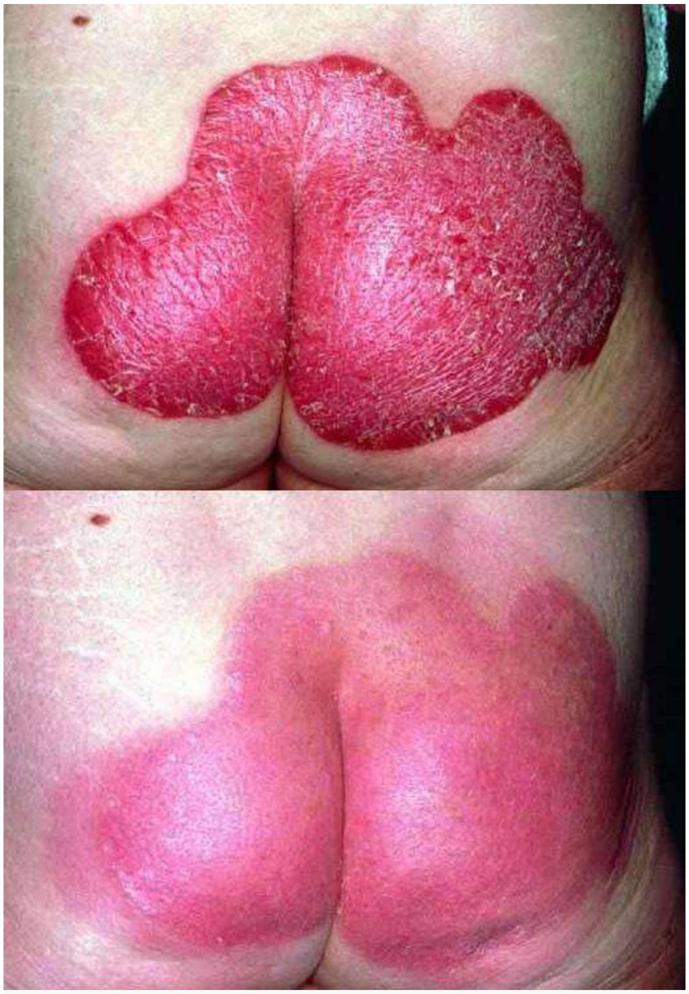


Using topical steroids in psoriasis

- as we know topical corticosteroid therapy may lead to skin atrophy, striae and rebound symptoms
- systemic side-effects may be seen when potent corticosteroids are used on large areas e.g. > 10% of the body surface area
- NICE recommend that we aim for a 4 week break before starting another course of topical corticosteroids
- they also recommend using potent corticosteroids for no longer than 8 weeks at a time and very potent corticosteroids for no longer than 4 weeks at a time

What should I know about vitamin D analogues?

- examples of vitamin D analogues include calcipotriol (Dovonex), calcitriol and tacalcitol
- they work by reducing cell division and differentiation
- adverse effects are uncommon
- unlike corticosteroids they may be used long-term
- unlike coal tar and dithranol they do not smell or stain
- they tend to reduce the scale and thickness of plaques but not the erythema
- they should be avoided in pregnancy
- the maximum weekly amount for adults is 100g



A 'before and after' image showing the effect of 6 weeks of calcipotriol therapy on a large plaque. Note how the scale has improved but the erythema remains

Steroids in psoriasis

- topical steroids are commonly used in flexural psoriasis and there is also a role for mild steroids in facial psoriasis. If steroids are ineffective for these conditions vitamin D analogues or tacrolimus ointment should be used second line
- patients should have 4 week breaks between course of topical steroids
- very potent steroids should not be used for longer than 4 weeks at a time. Potent steroids can be used for up to 8 weeks at a time
- the scalp, face and flexures are particularly prone to steroid atrophy so topical steroids should not be used for more than 1-2 weeks/month

Scalp psoriasis

- NICE recommend the use of potent topical corticosteroids used once daily for 4 weeks
- if no improvement after 4 weeks then either use a different formulation of the potent corticosteroid (for example, a shampoo or mousse) and/or a topical agents to remove adherent scale (for example, agents containing salicylic acid, emollients and oils) before application of the potent corticosteroid

Face, flexutal and genital psoriasis

- NICE recommend offering a mild or moderate potency corticosteroid applied once or twice daily for a maximum of 2 weeks

**Secondary care management**

Phototherapy

- narrow band ultraviolet B light is now the treatment of choice. If possible this should be given 3 times a week
- photochemotherapy is also used - psoralen + ultraviolet A light (PUVA)
- adverse effects: skin ageing, squamous cell cancer (not melanoma)

Systemic therapy

- oral methotrexate is used first-line. It is particularly useful if there is associated joint disease
- ciclosporin
- systemic retinoids
- biological agents: infliximab, etanercept and adalimumab
- ustekinumab (IL-12 and IL-23 blocker) is showing promise in early trials

Mechanism of action of commonly used drugs:

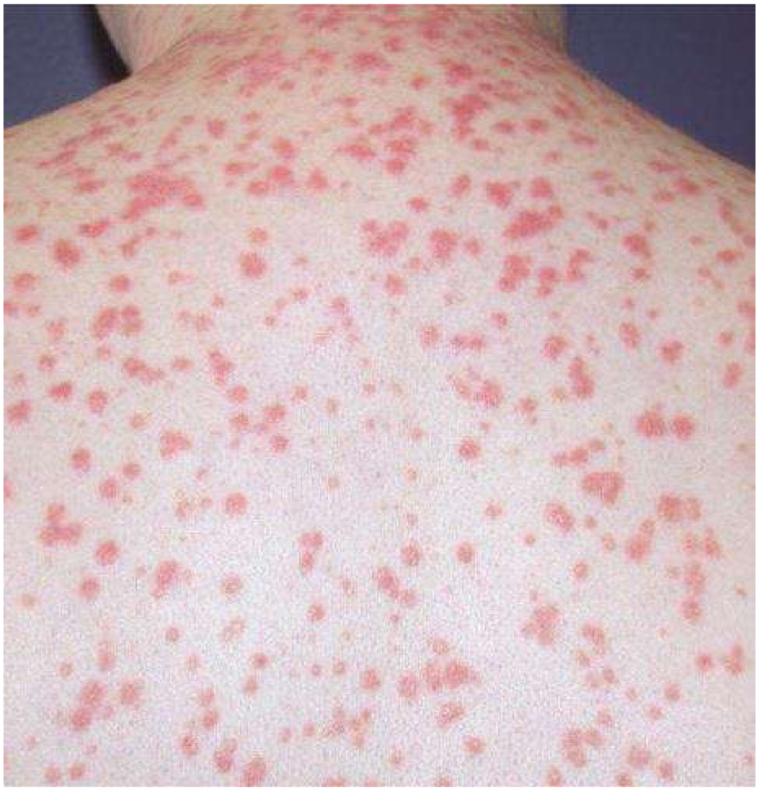
- coal tar: probably inhibit DNA synthesis
- calcipotriol: vitamin D analogue which reduces epidermal proliferation and restores a normal horny layer
- dithranol: inhibits DNA synthesis, wash off after 30 mins, SE: burning, staining

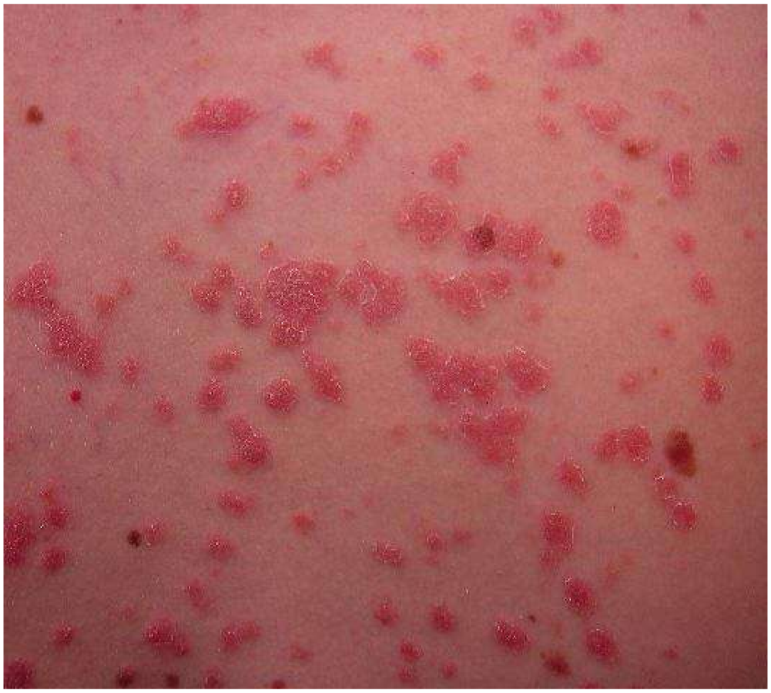
# GUTTATE PSORIASIS

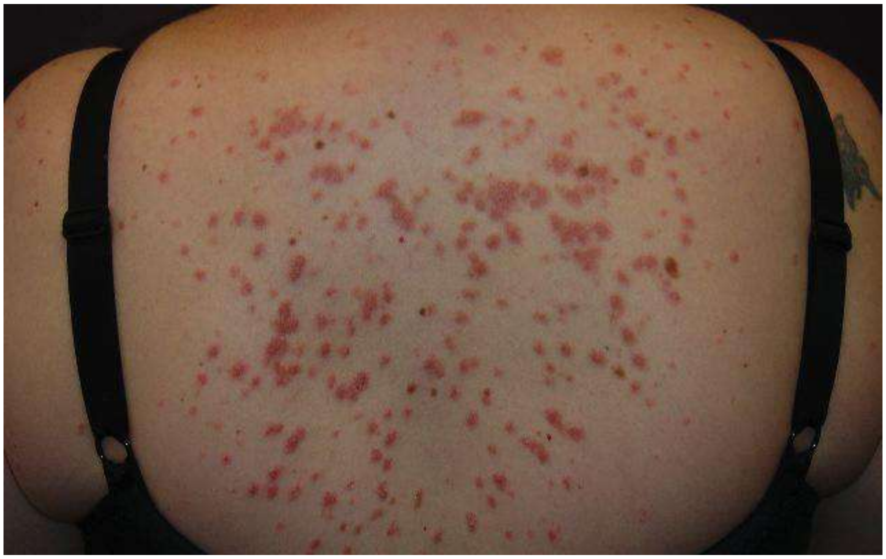
Guttate psoriasis is more common in children and adolescents. It may be precipitated by a streptococcal infection 2-4 weeks prior to the lesions appearing.

Features

- tear drop papules on the trunk and limbs







Management

- most cases resolve spontaneously within 2-3 months
- there is no firm evidence to support the use of antibiotics to eradicate streptococcal infection
- topical agents as per psoriasis
- UVB phototherapy
- tonsillectomy may be necessary with recurrent episodes

**Differentiating guttate psoriasis and pityriasis rosea**

| | Guttate psoriasis | Pityriasis rosea |
|---|---|---|
| **Prodrome** | Classically preceded by a streptococcal sore throat 2-4 weeks | Many patients report recent respiratory tract infections but this is not common in questions |
| **Appearance** | 'Tear drop', scaly papules on the trunk and limbs | Herald patch followed 1-2 weeks later by multiple erythematous, slightly raised oval lesions with a fine scale confined to the outer aspects of the lesions.<br><br>May follow a characteristic distribution with the longitudinal diameters of the oval lesions running parallel to the line of Langer. This may produce a 'fir-tree' appearance |
| **Treatment / natural history** | Most cases resolve spontaneously within 2-3 months<br>Topical agents as per psoriasis<br>UVB phototherapy | Self-limiting, resolves after around 6 weeks |

# PITYRIASIS ROSEA

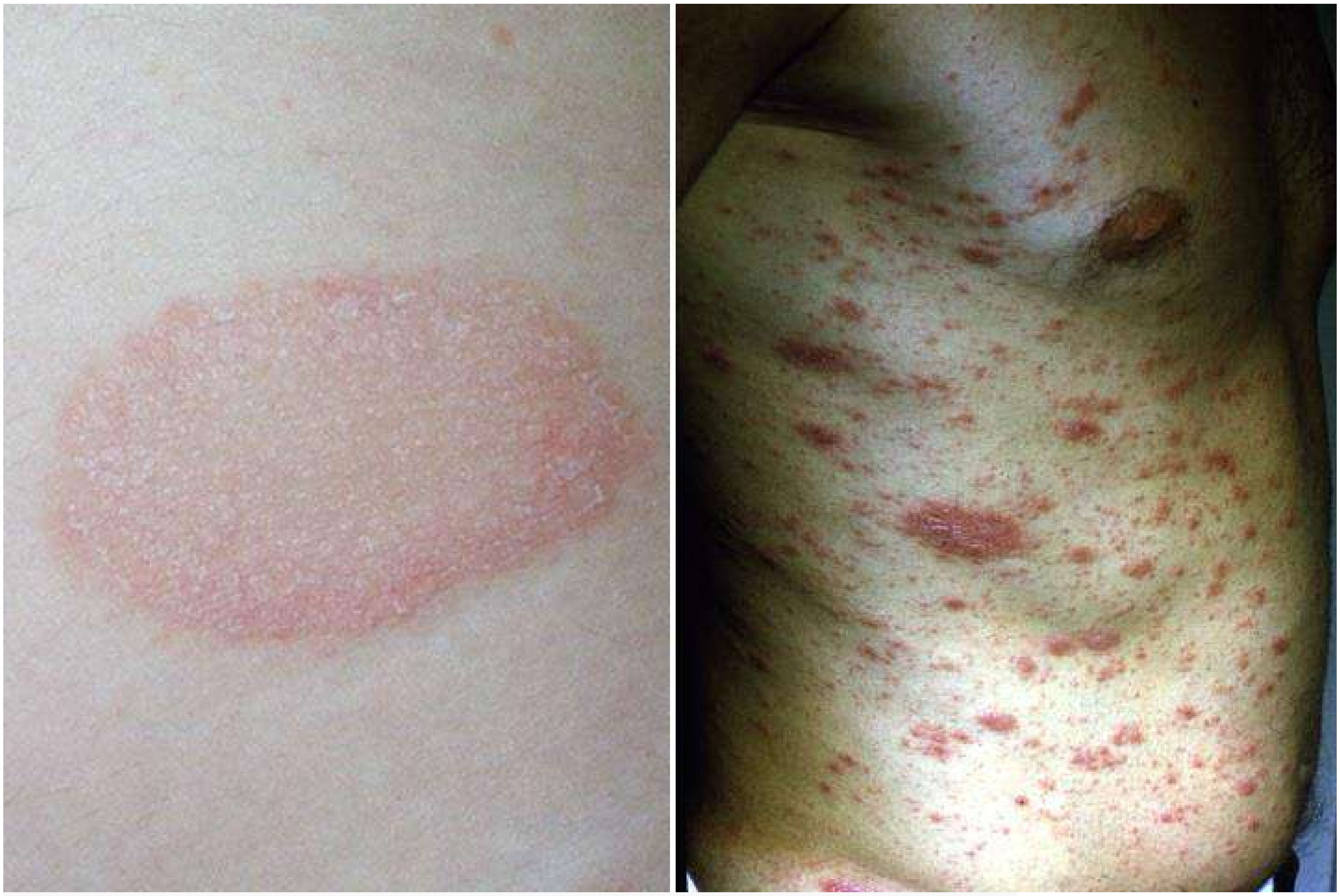
Pityriasis rosea describes an acute, self-limiting rash which tends to affect young adults. The aetiology is not fully understood but is thought that herpes hominis virus 7 (HHV-7) may play a role.

Features

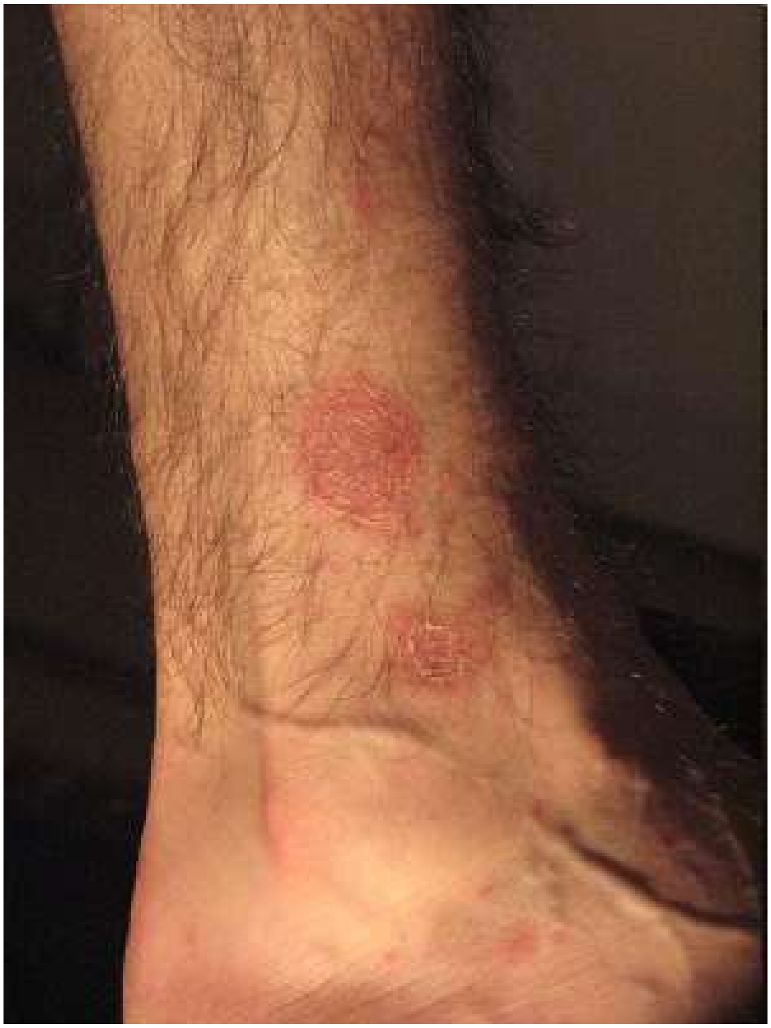
- in the majority of patients there is no prodrome, but a minority may give a history of a recent viral infection
- herald patch (usually on trunk)
- followed by erythematous, oval, scaly patches which follow a characteristic distribution with the longitudinal diameters of the oval lesions running parallel to the line of Langer. This may produce a 'fir-tree' appearance

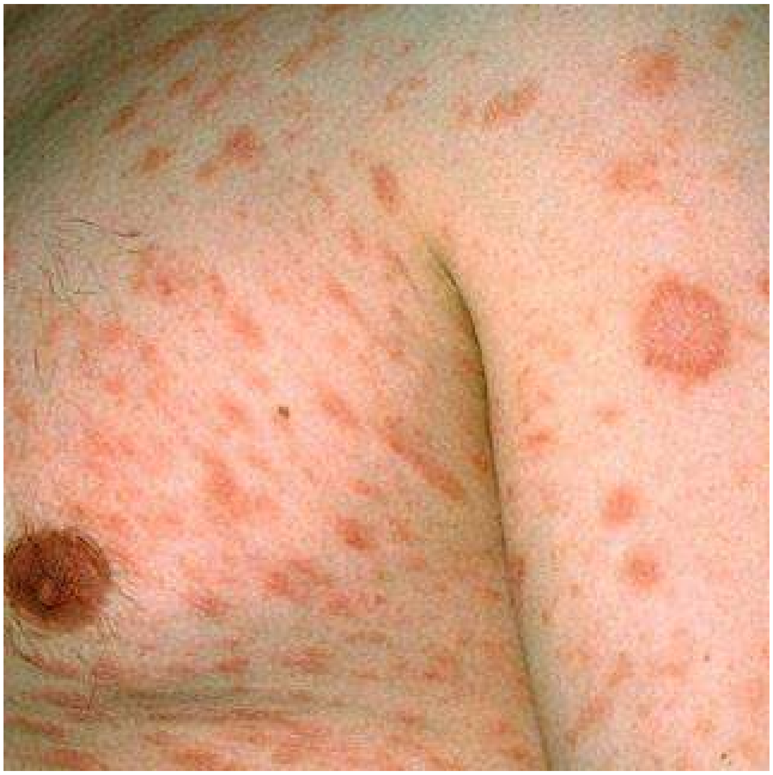
Management

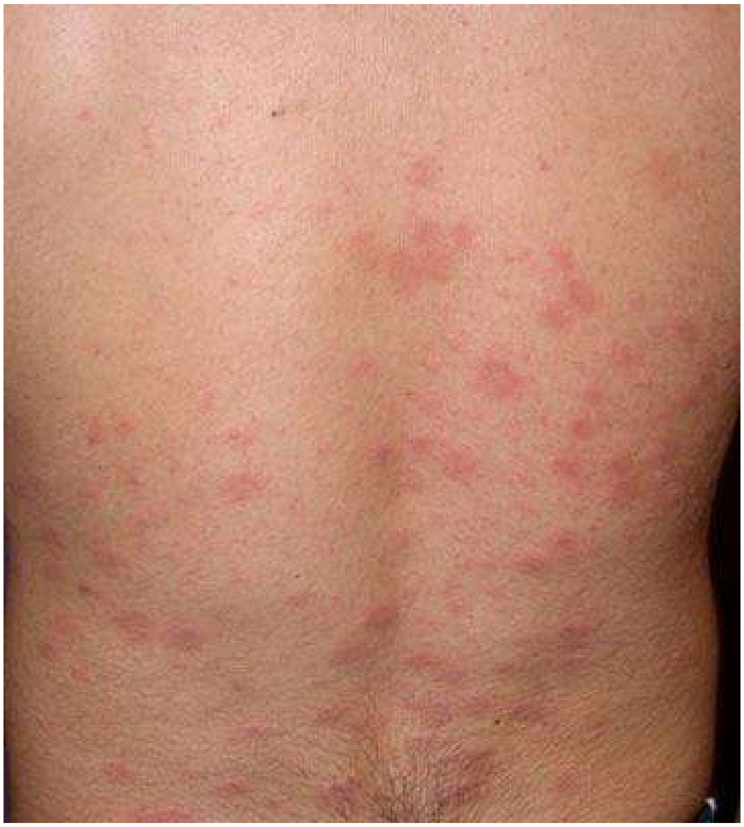
- self-limitingm - usually disappears after 6-12 weeks



On the left a typical herald patch is seen. After a few days a more generalised 'fir-tree' rash appears







## PITYRIASIS VERSICOLOR

Pityriasis versicolor, also called tinea versicolor, is a superficial cutaneous fungal infection caused by Malassezia furfur (formerly termed Pityrosporum ovale)

Features
- most commonly affects trunk
- patches may be hypopigmented, pink or brown (hence versicolor). May be more noticeable following a suntan
- scale is common
- mild pruritus

Predisposing factors
- occurs in healthy individuals
- immunosuppression
- malnutrition
- Cushing's

Management
- topical antifungal. NICE Clinical Knowledge Summaries advise ketoconazole shampoo as this is more cost effective for large areas
- if failure to respond to topical treatment then consider alternative diagnoses (e.g. send scrapings to confirm the diagnosis) + oral itraconazole

# PORPHYRIA CUTANEA TARDA

Porphyria cutanea tarda is the most common hepatic porphyria. It is due to an inherited defect in uroporphyrinogen decarboxylase or caused by hepatocyte damage e.g. alcohol, hepatitis C, oestrogen.

Features

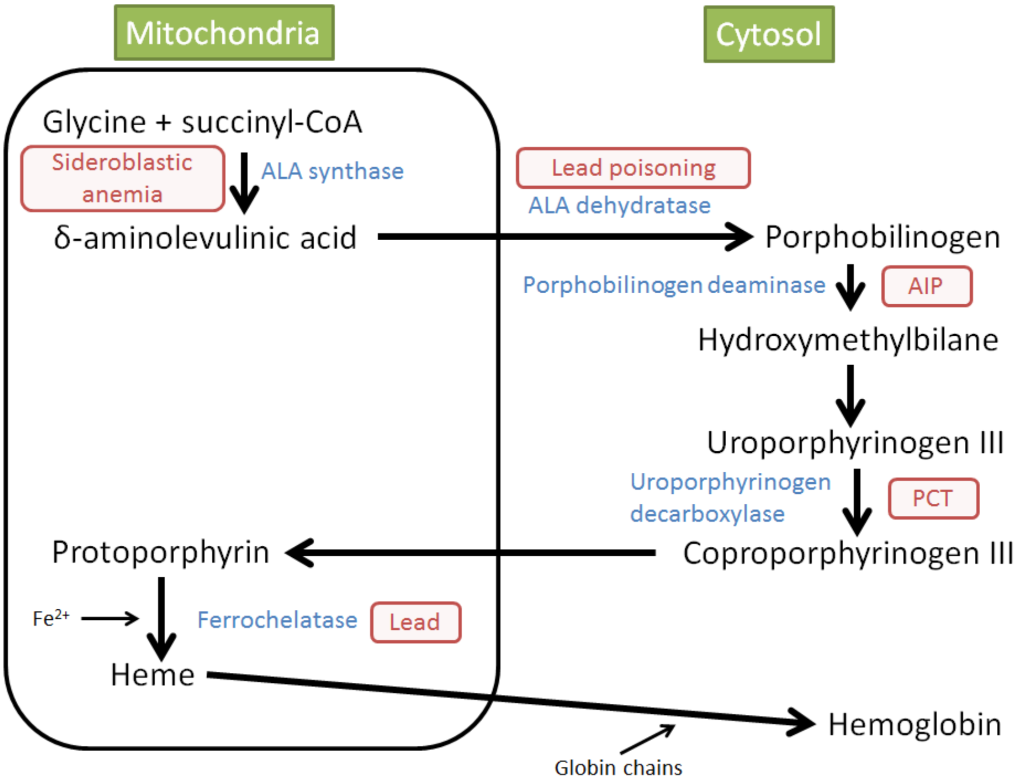
- classically presents with photosensitive rash with blistering and skin fragility on the face and dorsal aspect of hands (most common feature)
- hypertrichosis
- hyperpigmentation

Investigations

- urine: elevated uroporphyrinogen and pink fluorescence of urine under Wood's lamp
- serum iron ferritin level is used to guide therapy

Management

- chloroquine
- venesection
    - preferred if iron ferritin is above 600 ng/ml


Mitochondria
Cytosol
Glycine + succinyl-CoA
Sideroblastic anemia
ALA synthase
δ-aminolevulinic acid
Lead poisoning
ALA dehydratase
Porphobilinogen
Porphobilinogen deaminase
AIP
Hydroxymethylbilane
Uroporphyrinogen III
Uroporphyrinogen decarboxylase
PCT
Coproporphyrinogen III
Protoporphyrin
Fe2+
Ferrochelatase
Lead
Heme
Hemoglobin
Globin chains

# SEBORRHOEIC DERMATITIS IN ADULTS

Seborrhoeic dermatitis in adults is a chronic dermatitis thought to be caused by an inflammatory reaction related to a proliferation of a normal skin inhabitant, a fungus called Malassezia furfur (formerly known as Pityrosporum ovale). It is common, affecting around 2% of the general population.

Features
- eczematous lesions on the sebum-rich areas: scalp (may cause dandruff), periorbital, auricular and nasolabial folds
- otitis externa and blepharitis may develop

Associated conditions include
- HIV
- Parkinson's disease

Scalp disease management
- over the counter preparations containing zinc pyrithione ('Head & Shoulders') and tar ('Neutrogena T/Gel') are first-line
- the preferred second-line agent is ketoconazole
- selenium sulphide and topical corticosteroid may also be useful

Face and body management
- topical antifungals: e.g. ketoconazole
- topical steroids: best used for short periods
- difficult to treat - recurrences are common

# CONTACT DERMATITIS

There are two main types of contact dermatitis
- irritant contact dermatitis: common - non-allergic reaction due to weak acids or alkalis (e.g. detergents). Often seen on the hands. Erythema is typical, crusting and vesicles are rare
- allergic contact dermatitis: type IV hypersensitivity reaction. Uncommon - often seen on the head following hair dyes. Presents as an acute weeping eczema which predominately affects the margins of the hairline rather than the hairy scalp itself. Topical treatment with a potent steroid is indicated

Cement is a frequent cause of contact dermatitis. The alkaline nature of cement may cause an irritant contact dermatitis whilst the dichromates in cement also can cause an allergic contact dermatitis

# NICKEL DERMATITIS

Nickel is a common cause allergic contact dermatitis and is an example of a type IV hypersensitivity reaction. It is often caused by jewellery such as watches

It is diagnosed by a skin patch test

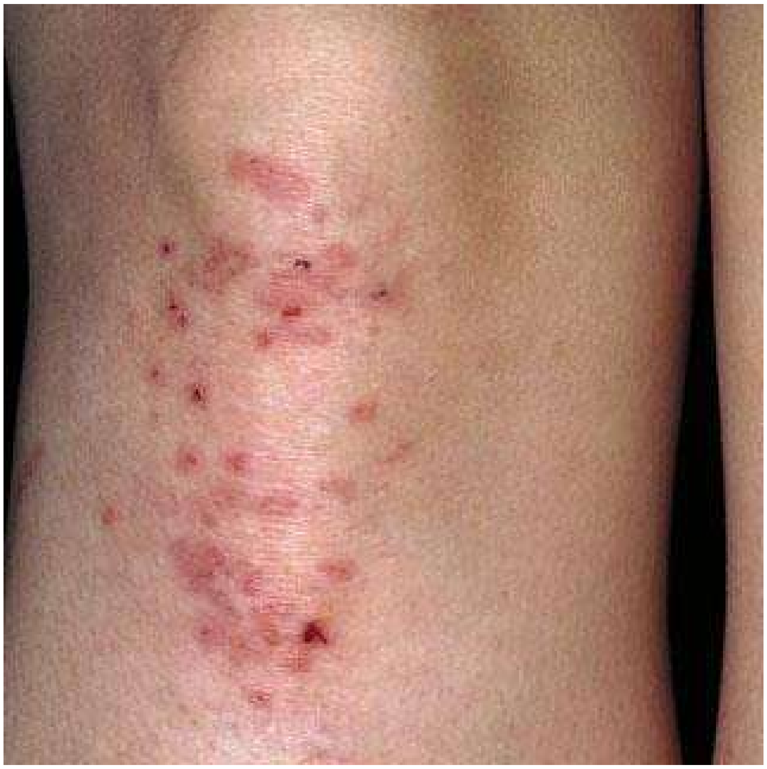
# DERMATITIS HERPETIFORMIS

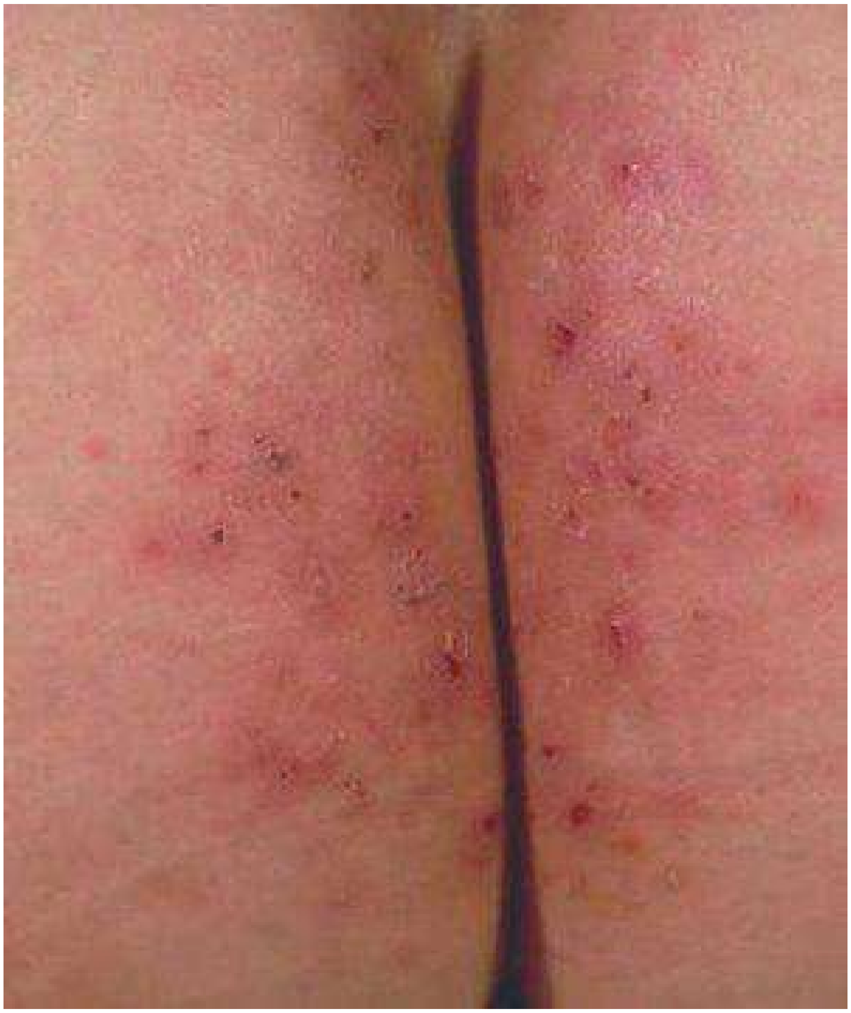
Dermatitis herpetiformis is an autoimmune blistering skin disorder associated with coeliac disease. It is caused by deposition of IgA in the dermis.

Features
- itchy, vesicular skin lesions on the extensor surfaces (e.g. elbows, knees, buttocks)

Diagnosis
- skin biopsy: direct immunofluorescence shows deposition of IgA in a granular pattern in the upper dermis

Management
- gluten-free diet
- dapsone





# ECZEMA HERPETICUM

Eczema herpeticum describes a severe primary infection of the skin by herpes simplex virus 1 or 2.

It is more commonly seen in children with atopic eczema and often presents as a rapidly progressing painful rash.

On examination, monomorphic punched-out erosions (circular, depressed, ulcerated lesions) usually 1–3 mm in diameter are typically seen.

As it is potentially life-threatening children should be admitted for IV aciclovir.

# ECZEMA: TOPICAL STEROIDS

Use weakest steroid cream which controls patients symptoms

The table below shows topical steroids by potency

| Mild | Moderate | Potent | Very potent |
|---|---|---|---|
| Hydrocortisone 0.5-2.5% | Betamethasone valerate 0.025% (Betnovate RD)<br>Clobetasone butyrate 0.05% (Eumovate) | Fluticasone propionate 0.05% (Cutivate)<br>Betamethasone valerate 0.1% (Betnovate) | Clobetasol propionate 0.05% (Dermovate) |

Finger tip rule

- 1 finger tip unit (FTU) = 0.5 g, sufficient to treat a skin area about twice that of the flat of an adult hand

Topical steroid doses for eczema in adults

| Area of skin | Fingertip units per dose |
|---|---|
| Hand and fingers (front and back) | 1.0 |
| A foot (all over) | 2.0 |
| Front of chest and abdomen | 7.0 |
| Back and buttocks | 7.0 |
| Face and neck | 2.5 |
| An entire arm and hand | 4.0 |
| An entire leg and foot | 8.0 |

The BNF makes recommendation on the quantity of topical steroids that should be prescribed for an adult for a single daily application for 2 weeks:

| Area | Amount |
|---|---|
| Face and neck | 15 to 30 g |
| Both hands | 15 to 30 g |
| Scalp | 15 to 30 g |
| Both arms | 30 to 60 g |
| Both legs | 100 g |
| Trunk | 100 g |
| Groin and genitalia | 15 to 30 g |

# POMPHOLYX

Pompholyx is a type of eczema which affects both the hands (cheiropompholyx) and the feet (pedopompholyx). It is also known as dyshidrotic eczema.

Pompholyx eczema may be precipitated by humidity (e.g. sweating) and high temperatures.

Features
- small blisters on the palms and soles
- pruritic
    - often intensely itchy
    - sometimes burning sensation
- once blisters burst skin may become dry and crack

Management
- cool compresses
- emollients
- topical steroids

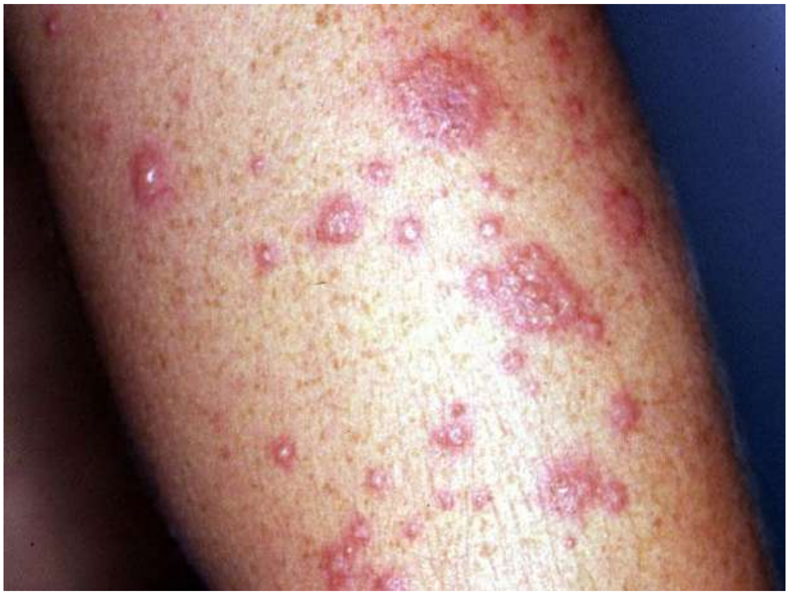
# ERYTHEMA MULTIFORME

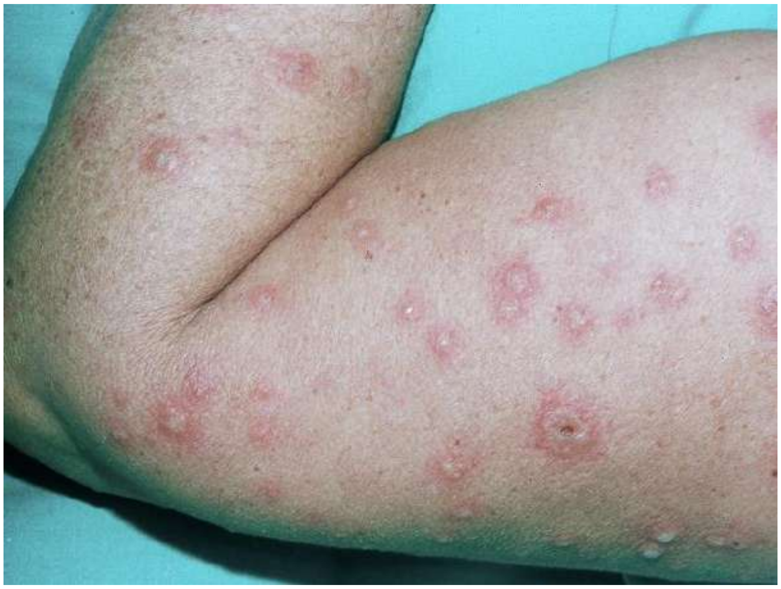
Erythema multiforme is a hypersensitivity reaction which is most commonly triggered by infections. It may be divided into minor and major forms.

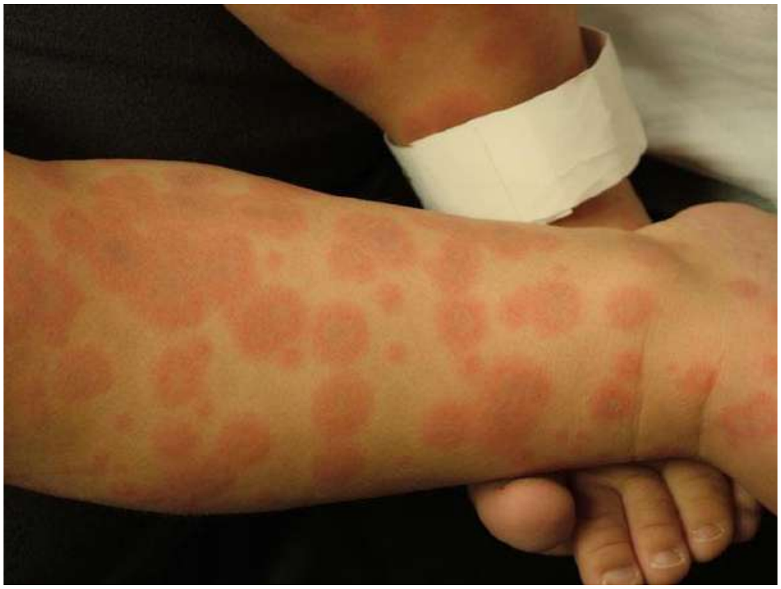
Previously it was thought that Stevens-Johnson syndrome (SJS) was a severe form of erythema multiforme. They are now however considered as separate entities.

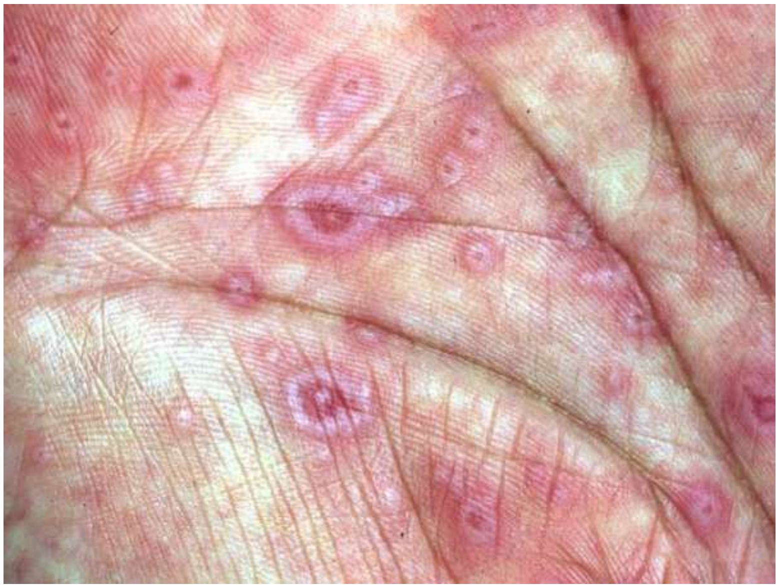
Features
- target lesions
- initially seen on the back of the hands / feet before spreading to the torso
- upper limbs are more commonly affected than the lower limbs
- pruritus is occasionally seen and is usually mild

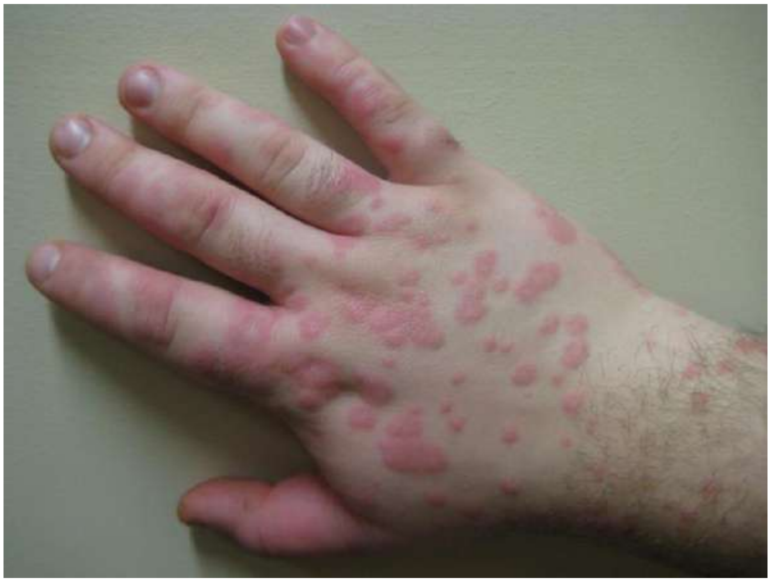
Causes
- viruses: herpes simplex virus (the most common cause), Orf*
- idiopathic
- bacteria: Mycoplasma, Streptococcus
- drugs: penicillin, sulphonamides, carbamazepine, allopurinol, NSAIDs, oral contraceptive pill, nevirapine
- connective tissue disease e.g. Systemic lupus erythematosus
- sarcoidosis
- malignancy





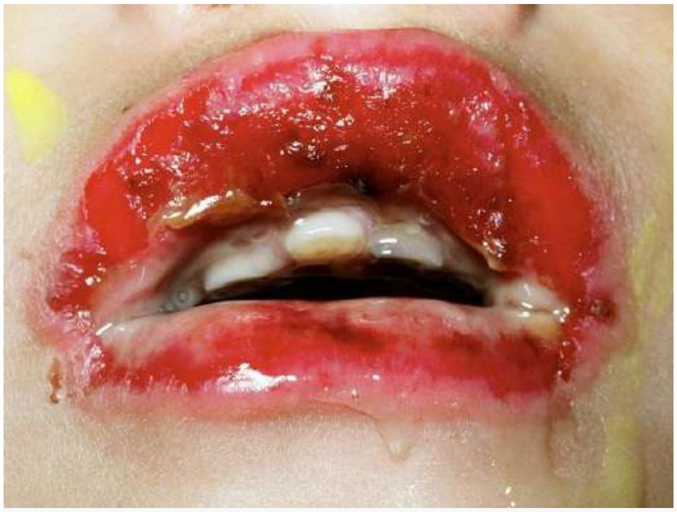






**Erythema multiforme major**

The more severe form, erythema multiforme major is associated with mucosal involvement.



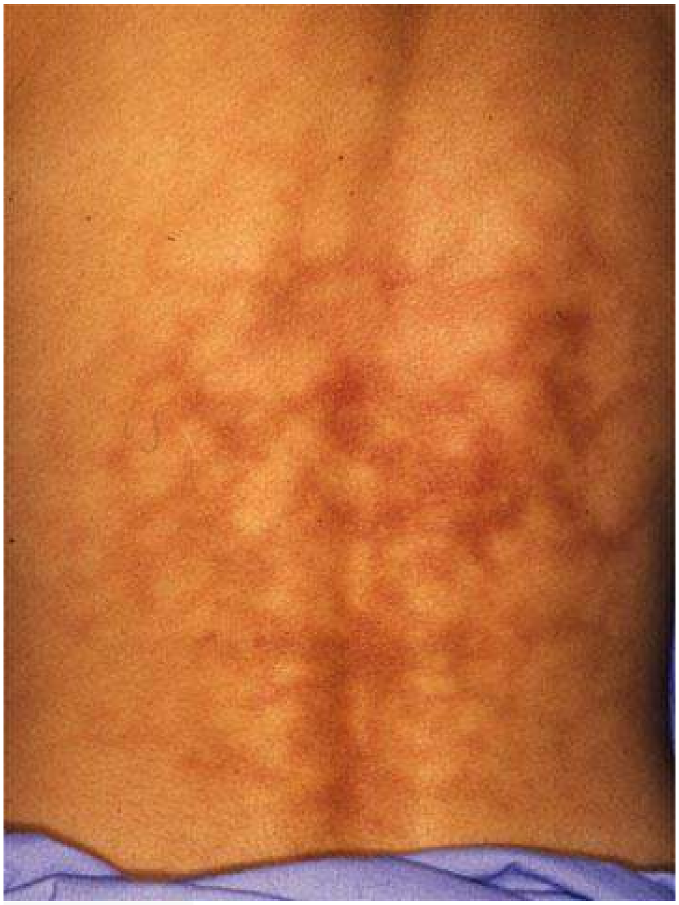
Example of mucosal involvement in erythema multiforme major

*Orf is a skin disease of sheep and goats caused by a parapox virus

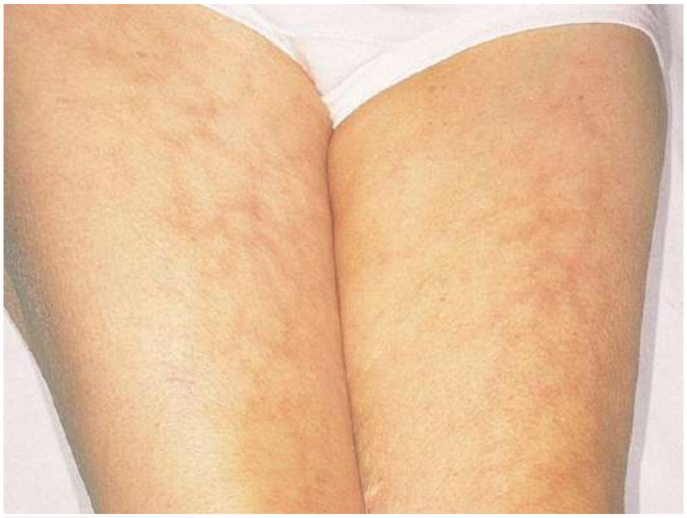
# ERYTHEMA AB IGNE

Erythema ab igne is a skin disorder caused by over exposure to infrared radiation. Characteristic features include reticulated, erythematous patches with hyperpigmentation and telangiectasia. A typical history would be an elderly women who always sits next to an open fire.

If the cause is not treated then patients may go on to develop squamous cell skin cancer.



Erythema ab igne



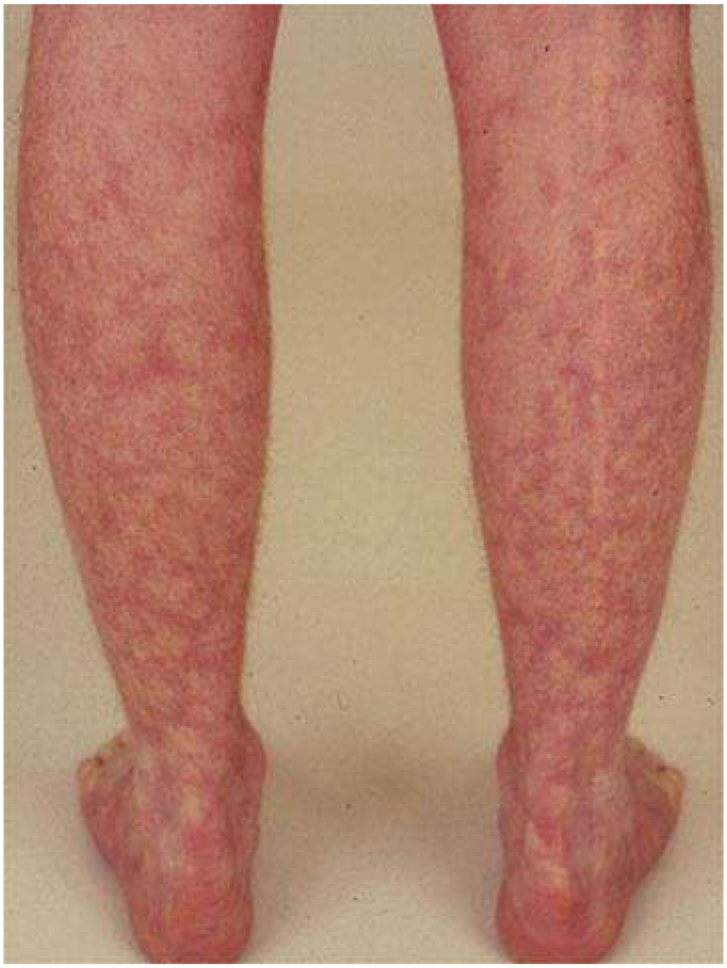
Erythema ab igne

# LIVEDO RETICULARIS

Livedo reticularis describes an purplish, non-blanching, reticulated rash caused by obstruction of the capillaries resulting in swollen venules.

Causes

- idiopathic (most common)
- polyarteritis nodosa
- systemic lupus erythematosus
- cryoglobulinaemia
- antiphospholipid syndrome
- Ehlers-Danlos Syndrome
- homocystinuria



# ERYTHRODERMA

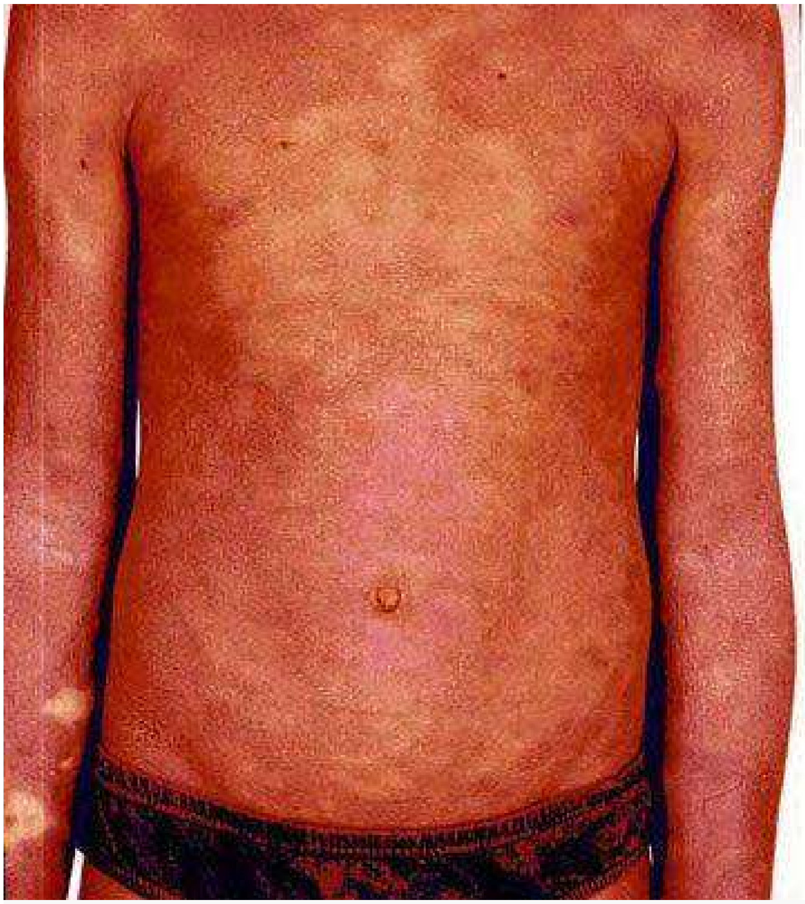
Erythroderma is a term used when more than 95% of the skin is involved in a rash of any kind.

Causes of erythroderma

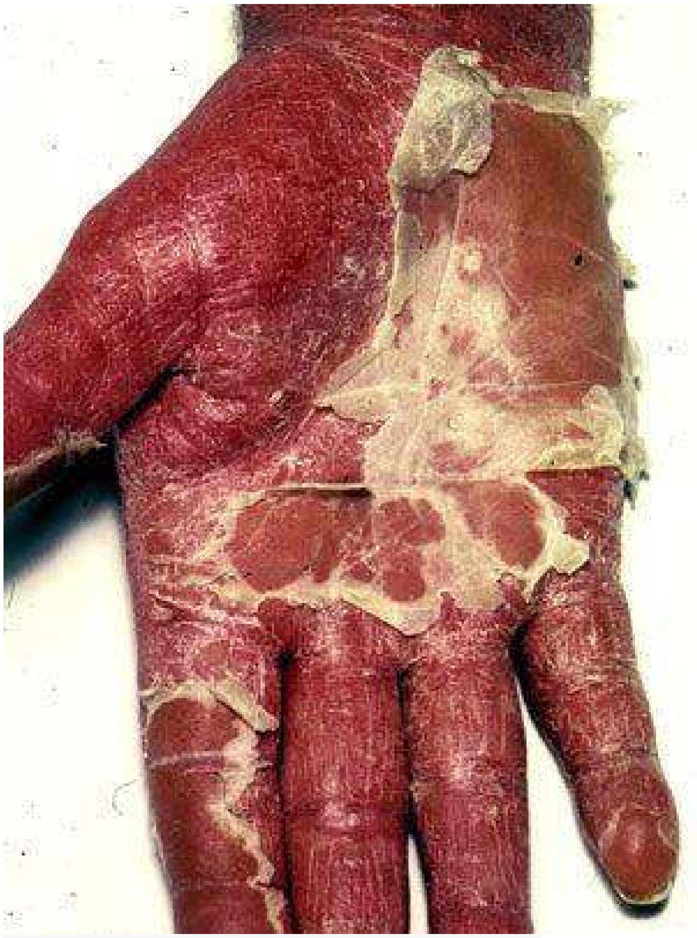
- eczema
- psoriasis
- drugs e.g. gold
- lymphomas, leukaemias
- idiopathic

Erythrodermic psoriasis

- may result from progression of chronic disease to an exfoliative phase with plaques covering most of the body. Associated with mild systemic upset
- more serious form is an acute deterioration. This may be triggered by a variety of factors such as withdrawal of systemic steroids. Patients need to be admitted to hospital for management\



This image shows the generalised erythematous rash seen in patients with erythroderma, sometimes referred to as 'red man syndrome'



Note the extensive exfoliation seen in this patient

## ERYTHRASMA

Erythrasma is a generally asymptomatic, flat, slightly scaly, pink or brown rash usually found in the groin or axillae. It is caused by an overgrowth of the diphtheroid Corynebacterium minutissimum

Examination with Wood's light reveals a coral-red fluorescence.

Topical miconazole or antibacterial are usually effective. Oral erythromycin may be used for more extensive infection

# TINEA

Tinea is a term given to dermatophyte fungal infections. Three main types of infection are described depending on what part of the body is infected

- tinea capitis - scalp
- tinea corporis - trunk, legs or arms
- tinea pedis - feet

Tinea capitis (scalp ringworm)

- a cause of scarring alopecia mainly seen in children
- if untreated a raised, pustular, spongy/boggy mass called a kerion may form
- most common cause is Trichophyton tonsurans in the UK and the USA
- may also be caused by Microsporum canis acquired from cats or dogs
- diagnosis: lesions due to Microsporum canis green fluorescence under Wood's lamp*. However the most useful investigation is scalp scrapings
- management (based on CKS guidelines): oral antifungals: terbinafine for Trichophyton tonsurans infections and griseofulvin for Microsporum infections. Topical ketoconazole shampoo should be given for the first two weeks to reduce transmission

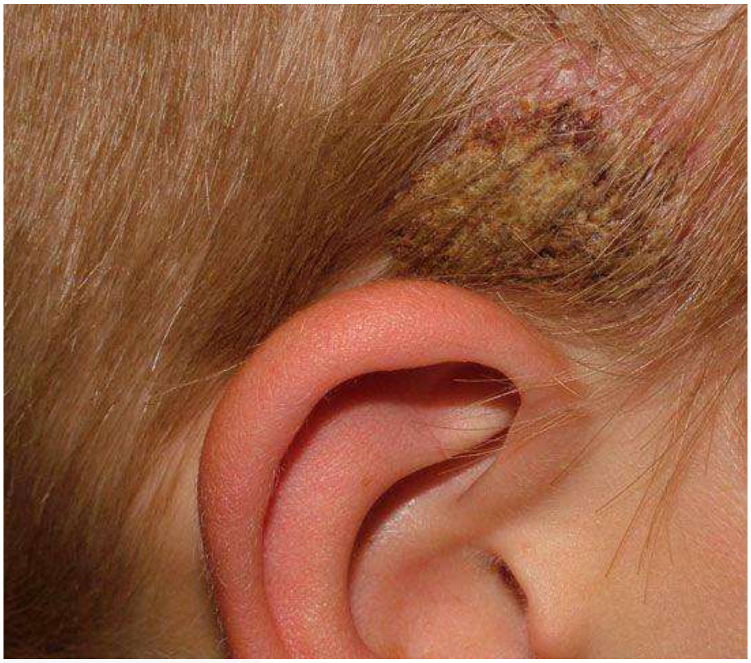


Image showing a kerion

Tinea corporis (ringworm)

- causes include Trichophyton rubrum and Trichophyton verrucosum (e.g. From contact with cattle)
- well-defined annular, erythematous lesions with pustules and papules
- may be treated with oral fluconazole

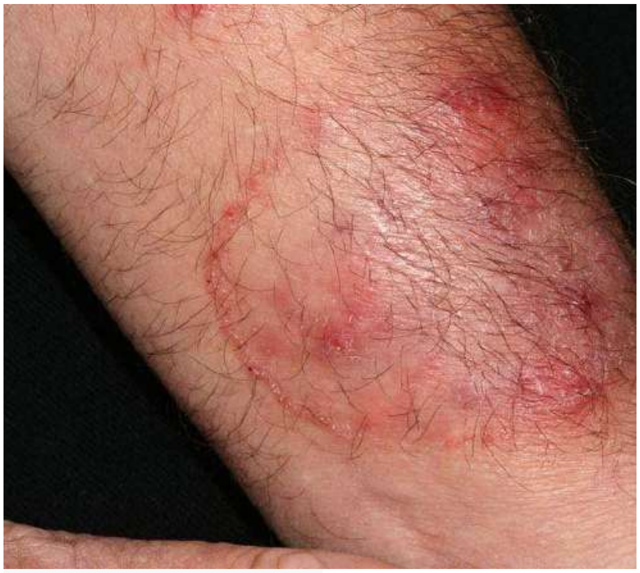


Image showing tinea corporis

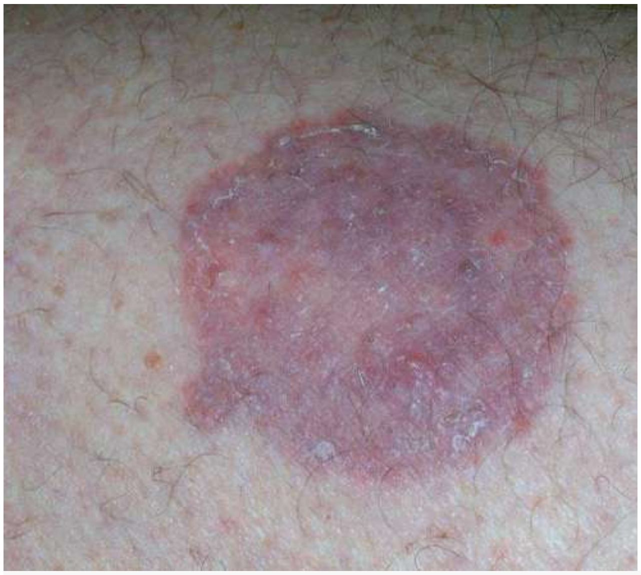


Image showing tinea corporis. Note the well defined border

Tinea pedis (athlete's foot)

- characterised by itchy, peeling skin between the toes
- common in adolescence

*lesions due to Trichophyton species do not readily fluoresce under Wood's lamp

# FUNGAL NAIL INFECTIONS

Onychomycosis is fungal infection of the nails. This may be caused by

- dermatophytes - mainly Trichophyton rubrum, accounts for 90% of cases
- yeasts - such as Candida
- non-dermatophyte moulds

Risk factors include for fungal nail infections include diabetes mellitus andincreasing age.

Features

- 'unsightly' nails are a common reason for presentation
- thickened, rough, opaque nails are the most common finding

Differential diagnosis

- psoriasis
- repeated trauma
- lichen planus
- yellow nail syndrome

Investigation

- nail clippings
- scrapings of the affected nail
- the false-negative rate for cultures are around 30%, so repeat samples may need to be sent if the clinical suspicion is high

Management

- do not need to be treated if it is asymptomatic and the patient is not bothered by the appearance
- diagnosis should be confirmed by microbiology before starting treatment
- dermatophyte infection:
  - oral terbinafine is currently recommended first-line with oral itraconazole as an alternative
  - 6 weeks - 3 months therapy is needed for fingernail infections whilst toenails should be treated for 3 - 6 months
  - treatment is successful in around 50-80% of people
- Candida infection:
  - mild disease should be treated with topical antifungals (e.g. Amorolfine) whilst more severe infections should be treated with oral itraconazole for a period of 12 weeks
- if topical topical treatment is given treatment should be continued for 6 months for fingernails and 9-12 months for toenails

# ONYCHOLYSIS

Onycholysis describes the separation of the nail plate from the nail bed

Causes
- idiopathic
- trauma e.g. Excessive manicuring
- infection: especially fungal
- skin disease: psoriasis, dermatitis
- impaired peripheral circulation e.g. Raynaud's
- systemic disease: hyper- and hypothyroidism

# YELLOW NAIL SYNDROME

Slowing of the nail growth leads to the characteristic thickened and discoloured nails seen in yellow nail syndrome.

Associations
- congenital lymphoedema
- pleural effusions
- bronchiectasis
- chronic sinus infections

# SCABIES

Scabies is caused by the mite Sarcoptes scabiei and is spread by prolonged skin contact. It typically affects children and young adults.

The scabies mite burrows into the skin, laying its eggs in the stratum corneum. The intense pruritus associated with scabies is due to a delayed-type IV hypersensitivity reaction to mites/eggs which occurs about 30 days after the initial infection.

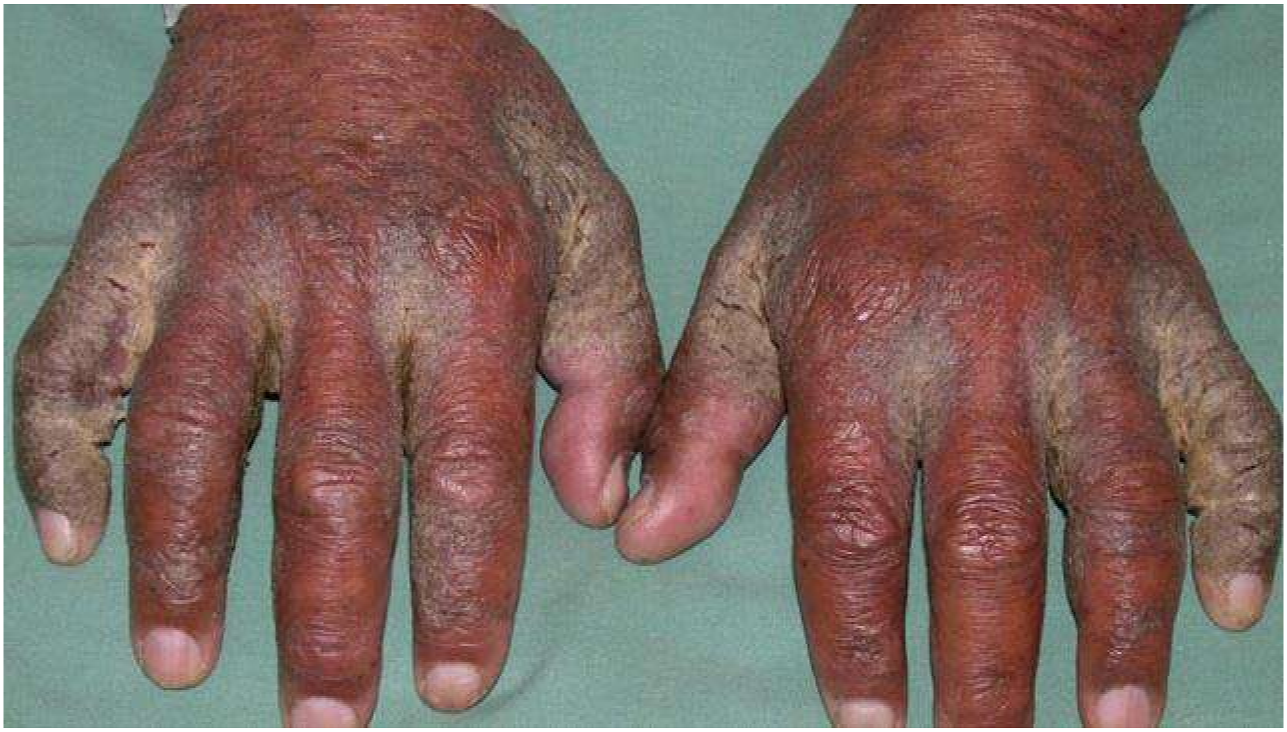
Features
- widespread pruritus
- linear burrows on the side of fingers, interdigital webs and flexor aspects of the wrist
- in infants, the face and scalp may also be affected
- secondary features are seen due to scratching: excoriation, infection

Management
- permethrin 5% is first-line
- malathion 0.5% is second-line
- give appropriate guidance on use (see below)
- pruritus persists for up to 4-6 weeks post eradication

Patient guidance on treatment (from Clinical Knowledge Summaries)
- avoid close physical contact with others until treatment is complete
- all household and close physical contacts should be treated at the same time, even if asymptomatic
- launder, iron or tumble dry clothing, bedding, towels, etc., on the first day of treatment to kill off mites.

The BNF advises to apply the insecticide to all areas, including the face and scalp, contrary to the manufacturer's recommendation. Patients should be given the following instructions:
- apply the insecticide cream or liquid to cool, dry skin
- pay close attention to areas between fingers and toes, under nails, armpit area, creases of the skin such as at the wrist and elbow
- allow to dry and leave on the skin for 8-12 hours for permethrin, or for 24 hours for malathion, before washing off
- reapply if insecticide is removed during the treatment period, e.g. If wash hands, change nappy, etc
- repeat treatment 7 days later

**Crusted (Norwegian) scabies**
Crusted scabies is seen in patients with suppressed immunity, especially HIV.



The crusted skin will be teeming with hundreds of thousands of organisms.

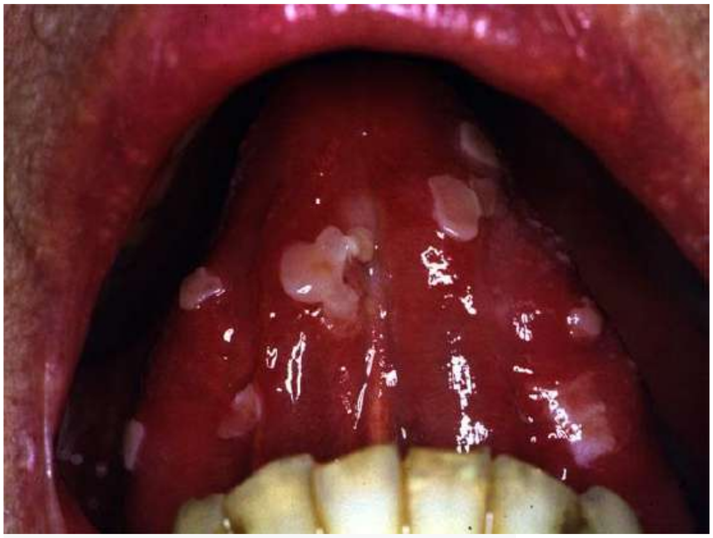
Ivermectin is the treatment of choice and isolation is essential

# PEMPHIGUS VULGARIS

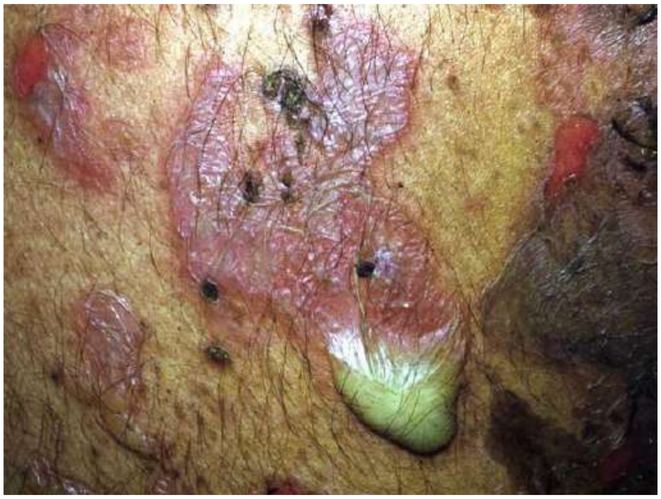
Pemphigus vulgaris is an autoimmune disease caused by antibodies directed against desmoglein 3, a cadherin-type epithelial cell adhesion molecule. It is more common in the Ashkenazi Jewish population.

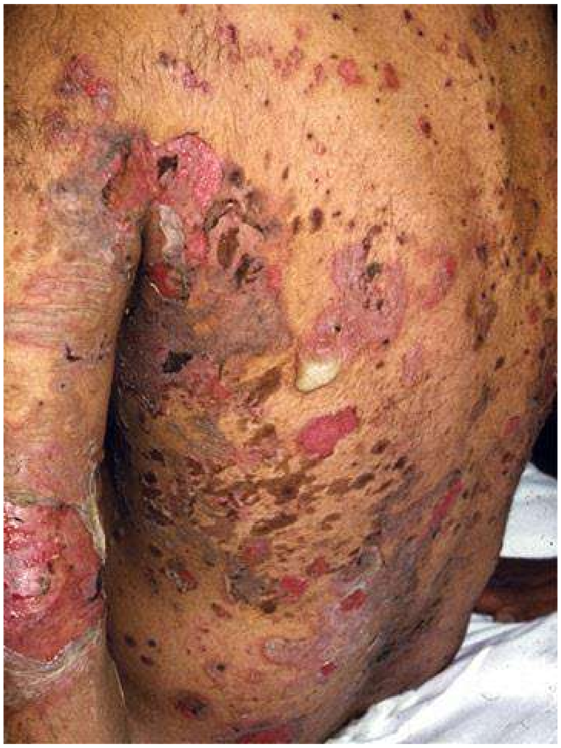
Features

- mucosal ulceration is common and often the presenting symptom. Oral involvement is seen in 50-70% of patients
- skin blistering - flaccid, easily ruptured vesicles and bullae. Lesions are typically painful but not itchy. These may develop months after the initial mucosal symptoms. Nikolsky's describes the spread of bullae following application of horizontal, tangential pressure to the skin
- acantholysis on biopsy



Mucosal ulceration is common with pemphigus





Management

- steroids are first-line
- immunosuppressants

# BULLOUS PEMPHIGOID

Bullous pemphigoid is an autoimmune condition causing sub-epidermal blistering of the skin. This is secondary to the development of antibodies against hemidesmosomal proteins BP180 and BP230

Bullous pemphigoid is more common in elderly patients. Features include

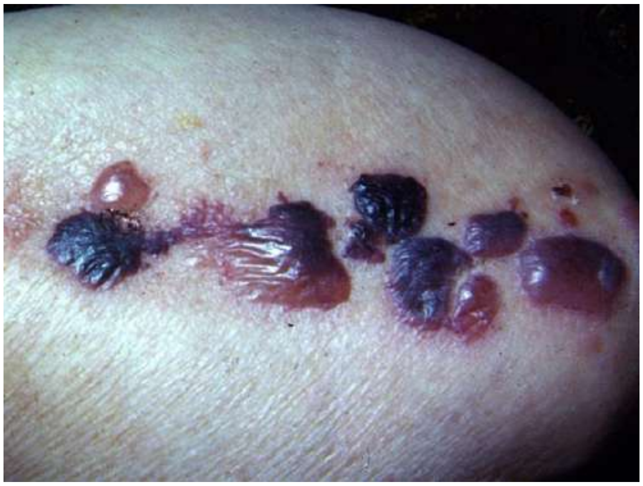
- itchy, tense blisters typically around flexures
- the blisters usually heal without scarring
- mouth is usually spared*

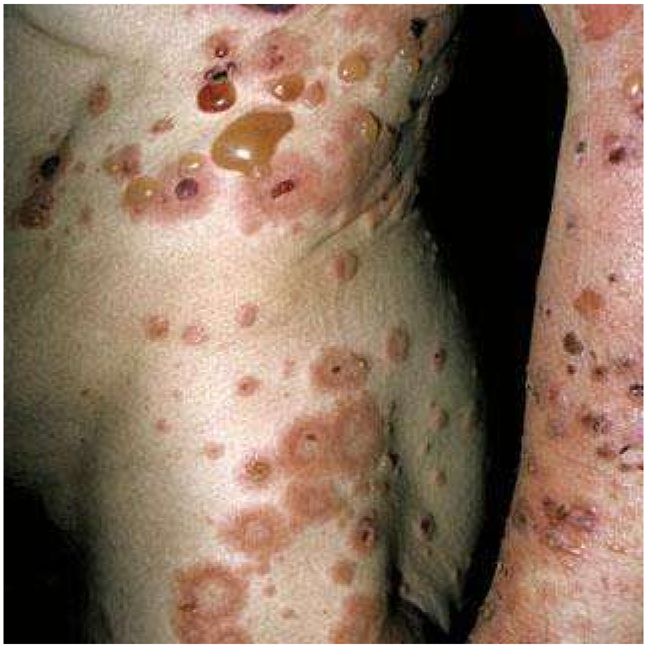
Skin biopsy

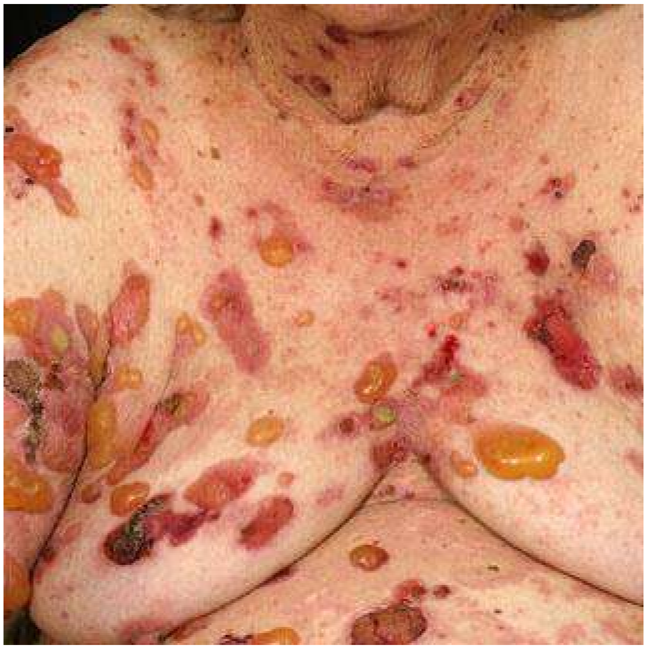
- immunofluorescence shows IgG and C3 at the dermoepidermal junction

Management

- referral to dermatologist for biopsy and confirmation of diagnosis
- oral corticosteroids are the mainstay of treatment
- topical corticosteroids, immunosuppressants and antibiotics are also used







*in reality around 10-50% of patients have a degree of mucosal involvement. It would however be unusual for an exam question to mention mucosal involvement as it is seen as a classic differentiating feature between pemphigoid and pemphigus.

# BASAL CELL CARCINOMA

Basal cell carcinoma (BCC) is one of the three main types of skin cancer. Lesions are also known as rodent ulcers and are characterised by slow-growth and local invasion. Metastases are extremely rare. BCC is the most common type of cancer in the Western world.

Features

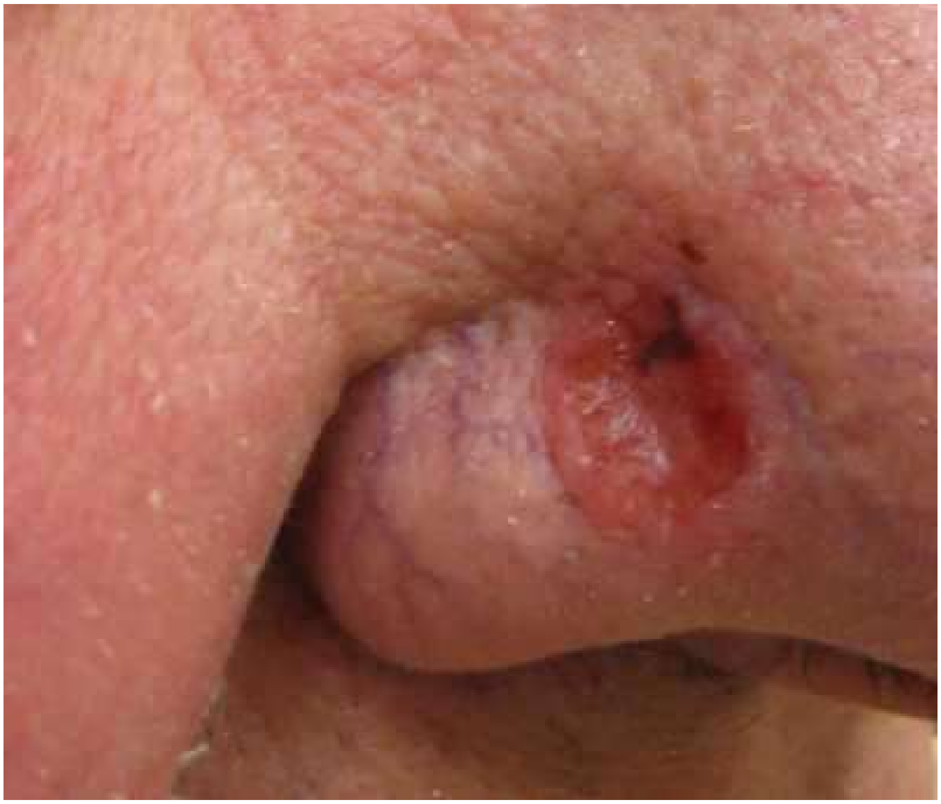
- many types of BCC are described. The most common type is nodular BCC, which is described here
- sun-exposed sites, especially the head and neck account for the majority of lesions
- initially a pearly, flesh-coloured papule with telangiectasia
- may later ulcerate leaving a central 'crater'

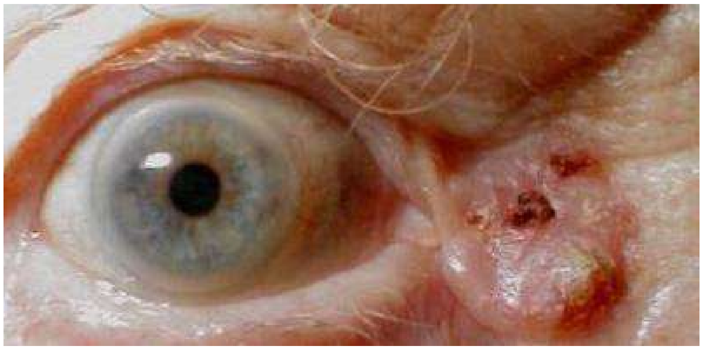
Referral

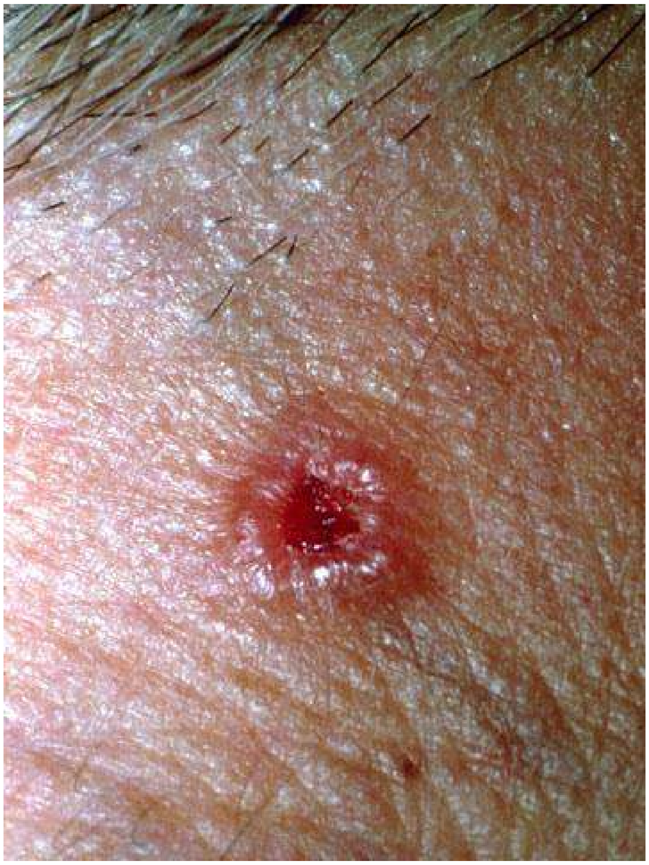
- generally, if a BCC is suspected, a routine referral should be made

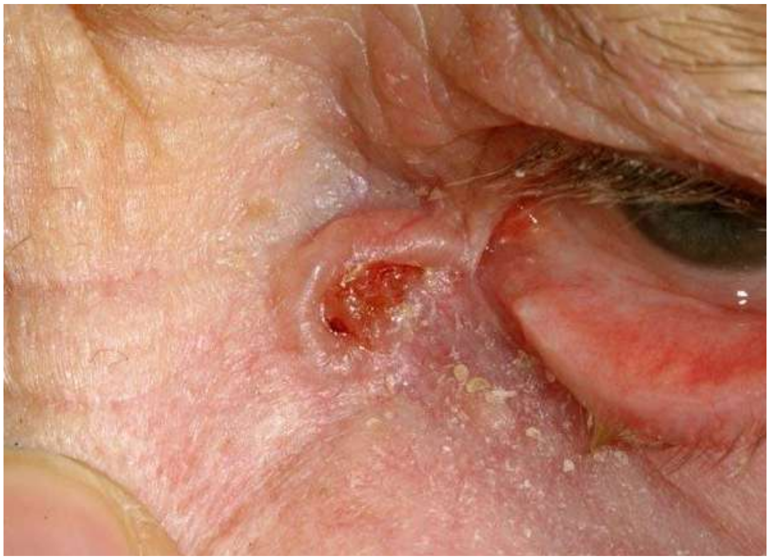
Management options:

- surgical removal
- curettage
- cryotherapy
- topical cream: imiquimod, fluorouracil
- radiotherapy









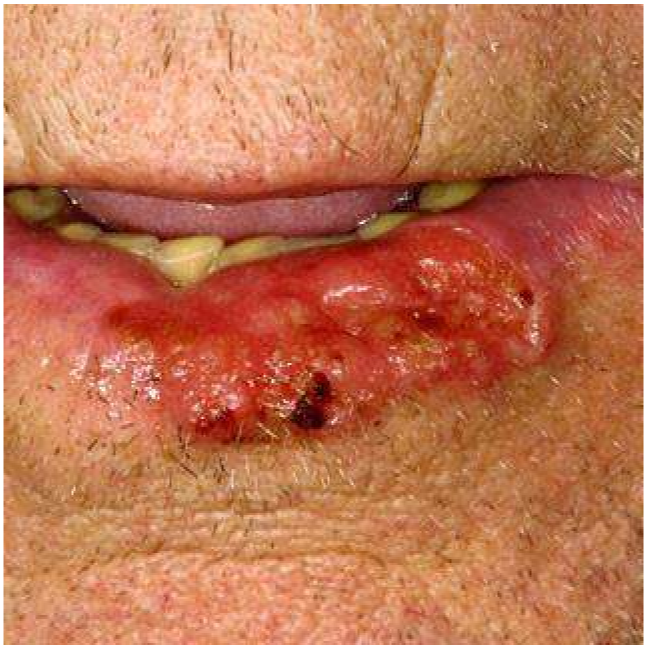
# SQUAMOUS CELL CARCINOMA OF THE SKIN

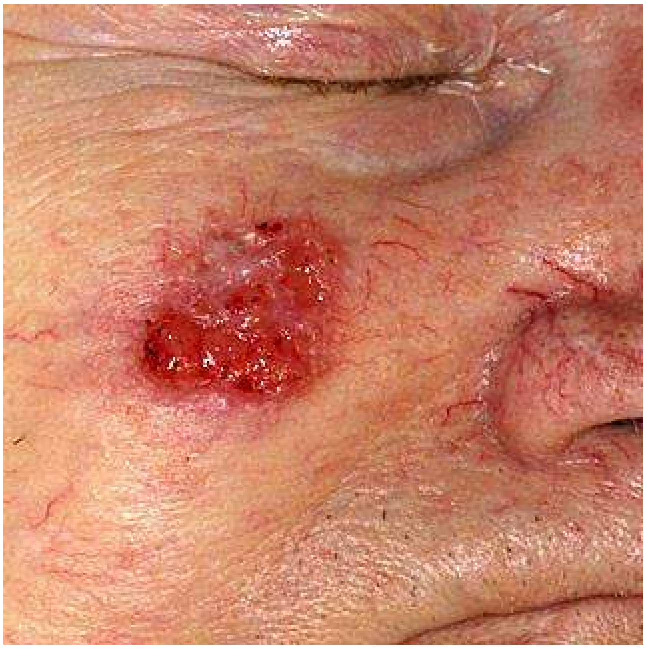
Squamous cell carcinoma is a common variant of skin cancer. Metastases are rare but may occur in 2-5% of patients.

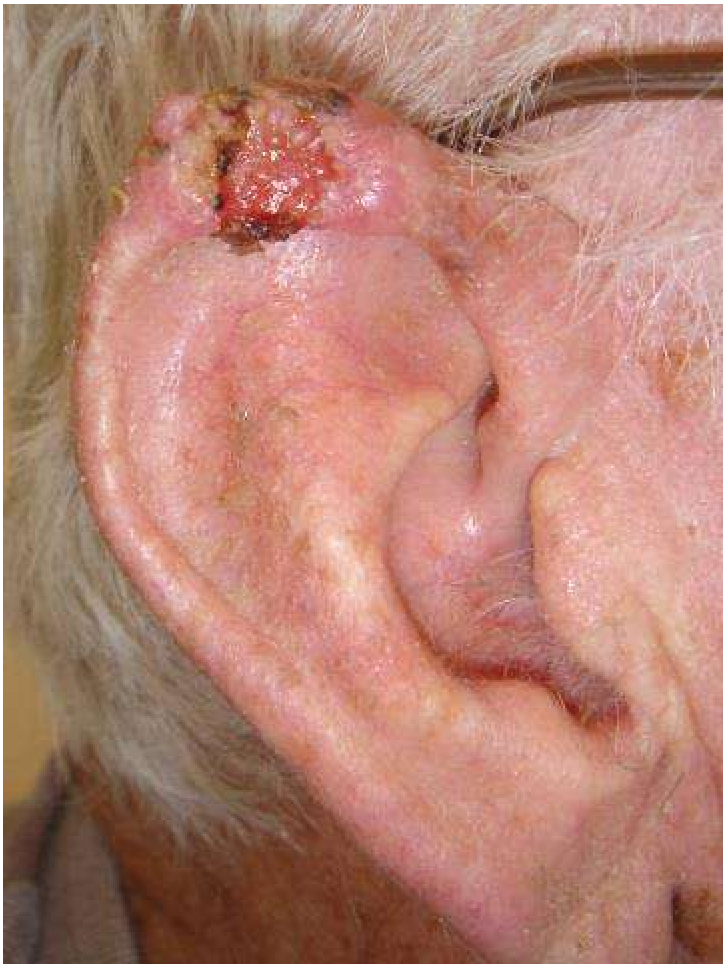
Risk factors include:

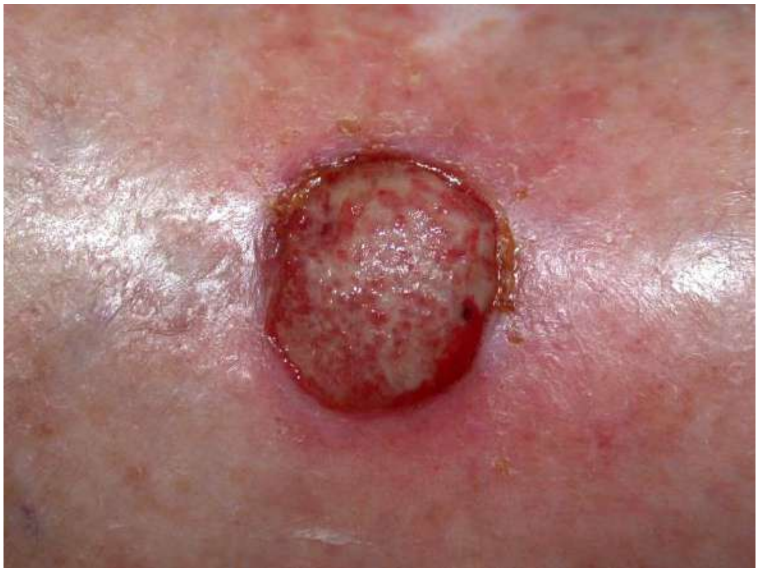
- excessive exposure to sunlight / psoralen UVA therapy
- actinic keratoses and Bowen's disease
- immunosuppression e.g. following renal transplant, HIV
- smoking
- long-standing leg ulcers (Marjolin's ulcer)
- genetic conditions e.g. xeroderma pigmentosum, oculocutaneous albinism

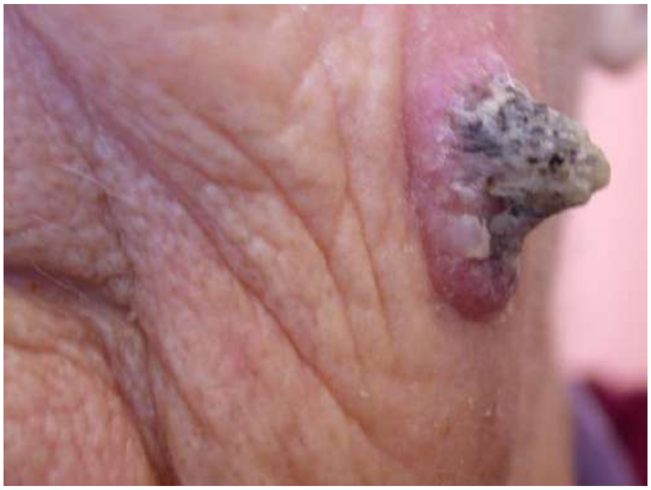
**Image gallery**

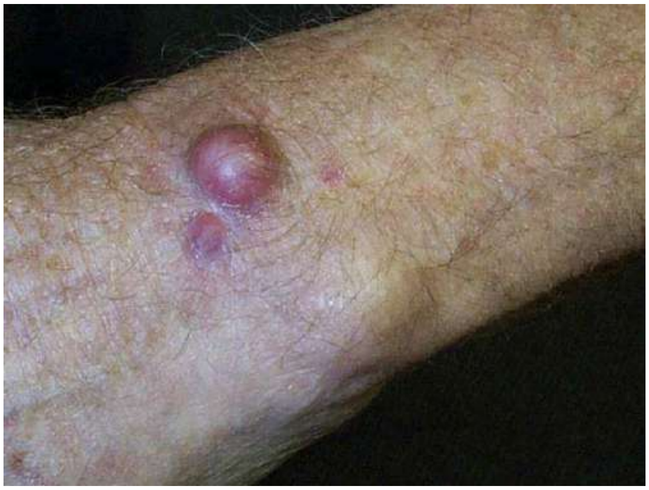












**Treatment**

Surgical excision with 4mm margins if lesion <20mm in diameter. If tumour >20mm then margins should be 6mm. Mohs micrographic surgery may be used in high-risk patients and in cosmetically important sites.

**Prognosis**

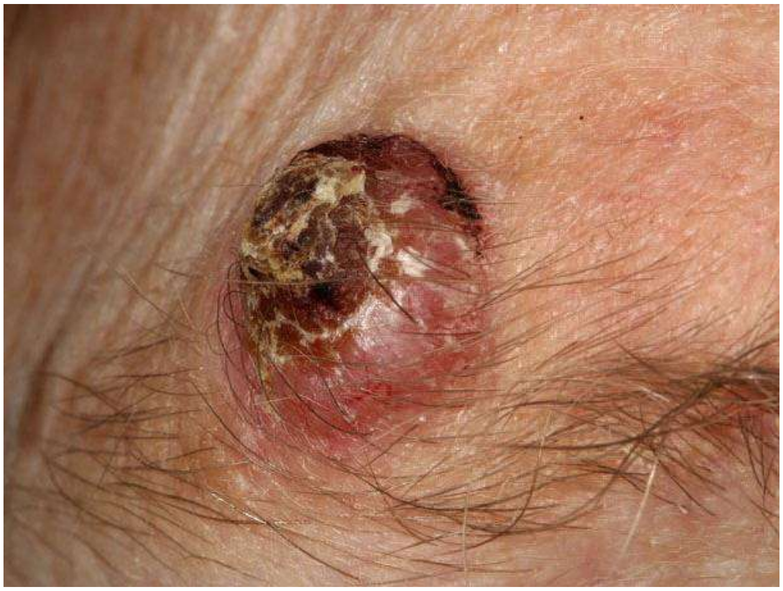
| Good Prognosis | Poor prognosis |
|---|---|
| Well differentiated tumours | Poorly differentiated tumours |
| <20mm diameter | >20mm in diameter |
| <2mm deep | >4mm deep |
| No associated diseases | Immunosupression for whatever reason |

# KERATOACANTHOMA

Keratoacanthoma is a benign epithelial tumour. They are more common with advancing age and rare in young people.

Features - said to look like a volcano or crater
- initially a smooth dome-shaped papule
- rapidly grows to become a crater centrally-filled with keratin

Spontaneous regression of keratoacanthoma within 3 months is common, often resulting in a scar. Such lesions should however be urgently excised as it is difficult clinically to exclude squamous cell carcinoma. Removal also may prevent scarring.



# MALIGNANT MELANOMA

There are four main subtypes of melanoma. Nodular melanoma is the most aggressive whilst the other forms spread more slowly.

| | Superficial spreading | Nodular | Lentigo maligna | Acral lentiginous |
|---|---|---|---|---|
| **Frequency** | 70% of cases | Second commonest | Less common | Rare form |
| **Typically affects** | Arms, legs, back and chest, young people | Sun exposed skin, middle-aged people | Chronically sun-exposed skin, older people | Nails, palms or soles, African Americans or Asians |
| **Appearance** | A growing moles with diagnostic features listed above | Red or black lump or lump which bleeds or oozes | A growing mole with diagnostic features listed above | Subungual pigmentation (Hutchinson's sign) or on palms or feet |

There are other rare forms of melanoma including desmoplastic melanoma, amelanotic melanoma, or melanoma arising in other parts of the body such as ocular melanoma.

| The main diagnostic features (major criteria): | Secondary features (minor criteria) |
|---|---|
| • Change in size<br>• Change in shape<br>• Change in colour | • Diameter >6mm<br>• Inflammation<br>• Oozing or bleeding<br>• Altered sensation |

### Treatment

- Suspicious lesions should undergo excision biopsy. The lesion should be removed in completely as incision biopsy can make subsequent histopathological assessment difficult.
- Once the diagnosis is confirmed the pathology report should be reviewed to determine whether further re-excision of margins is required (see below):

### Margins of excision-Related to Breslow thickness

| | |
|---|---|
| **Lesions 0-1mm thick** | 1cm |
| **Lesions 1-2mm thick** | 1- 2cm (Depending upon site and pathological features) |
| **Lesions 2-4mm thick** | 2-3 cm (Depending upon site and pathological features) |
| **Lesions >4 mm thick** | 3cm |

Further treatments such as sentinel lymph node mapping, isolated limb perfusion and block dissection of regional lymph node groups should be selectively applied.

# MALIGNANT MELANOMA: PROGNOSTIC FACTORS

The invasion depth of a tumour (Breslow depth) is the single most important factor in determining prognosis of patients with malignant melanoma

| Breslow Thickness | Approximate 5 year survival |
|---|---|
| < 1 mm | 95-100% |
| 1 - 2 mm | 80-96% |
| 2.1 - 4 mm | 60-75% |
| > 4 mm | 50% |

# LENTIGO MALIGNA

Lentigo maligna is a type of melanoma in-situ. It typically progresses slowly but may at some stage become invasive causing lentigo maligna melanoma.

# ACTINIC KERATOSES

Actinic, or solar, keratoses (AK) is a common premalignant skin lesion that develops as a consequence of chronic sun exposure

Features

- small, crusty or scaly, lesions
- may be pink, red, brown or the same colour as the skin
- typically on sun-exposed areas e.g. temples of head
- multiple lesions may be present

Management options include

- prevention of further risk: e.g. sun avoidance, sun cream
- fluorouracil cream: typically a 2 to 3 week course. The skin will become red and inflamed - sometimes topical hydrocortisone is given following fluorouracil to help settle the inflammation
- topical diclofenac: may be used for mild AKs. Moderate efficacy but much fewer side-effects
- topical imiquimod: trials have shown good efficacy
- cryotherapy
- curettage and cautery

# MYCOSIS FUNGOIDES

Mycosis fungoides is a rare form of T-cell lymphoma that affects the skin.

Features

- itchy, red patches which are

- lesions tend to be of different colours in contrast to eczema/psoriasis where there is greater homogenicity

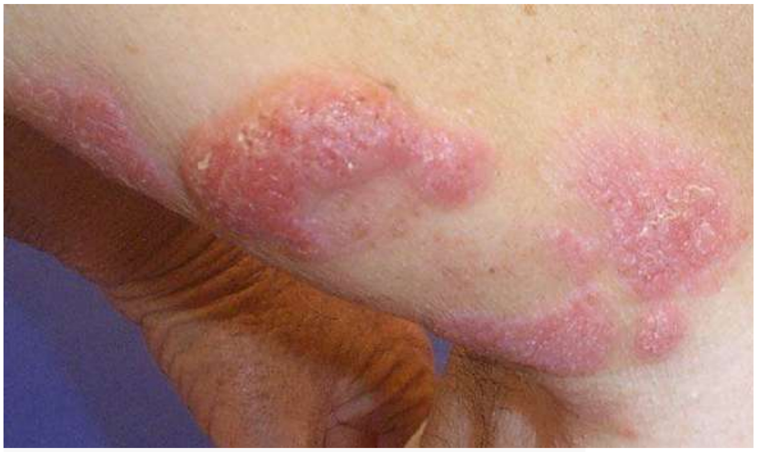
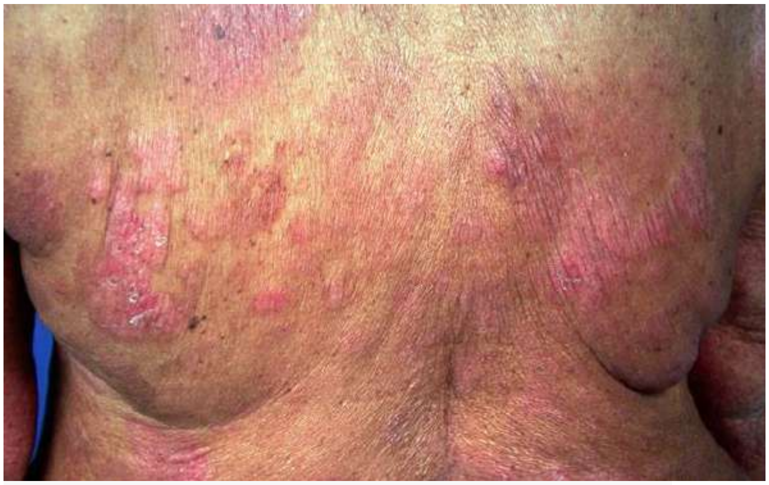


Image showing the plaque stage of mycosis fungoides



Further image showing the plaque stage of mycosis fungoides

## SEZARY SYNDROME

Sezary syndrome is a type of T-cell cutaenous lymphoma.

Features

- pruritus
- erythroderma typically affecting the palms, soles and face
- atypical T cells
- lymphadenopathy
- hepatosplenomegaly

# SKIN DISORDERS ASSOCIATED WITH DIABETES

Note whilst pyoderma gangrenosum can occur in diabetes mellitus it is rare and is often not included in a differential of potential causes

Necrobiosis lipoidica

- shiny, painless areas of yellow/red/brown skin typically on the shin
- often associated with surrounding telangiectasia

Infection

- candidiasis
- staphylococcal

Neuropathic ulcers

Vitiligo

Lipoatrophy

Granuloma annulare*

- papular lesions that are often slightly hyperpigmented and depressed centrally

*it is not clear from recent studies if there is actually a significant association between diabetes mellitus and granuloma annulare, but it is often listed in major textbooks

# ACANTHOSIS NIGRICANS

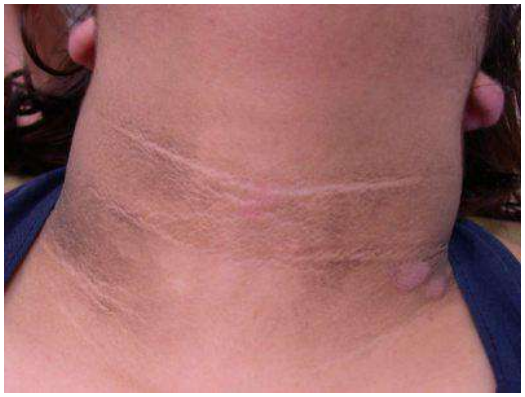
Describes symmetrical, brown, velvety plaques that are often found on the neck, axilla and groin.

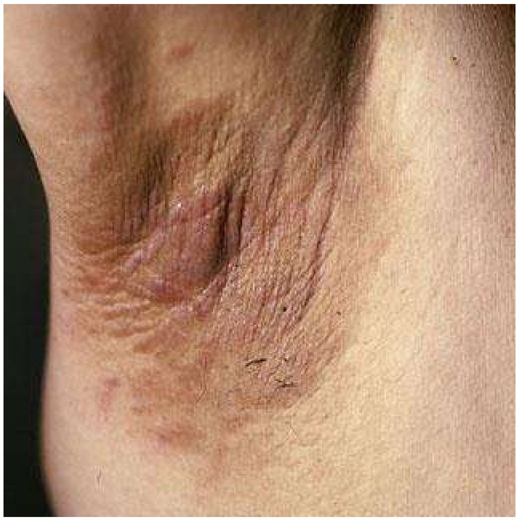
Causes

- type 2 diabetes mellitus
- gastrointestinal cancer
- obesity
- polycystic ovarian syndrome
- acromegaly
- Cushing's disease
- hypothyroidism
- familial
- Prader-Willi syndrome
- drugs: oral contraceptive pill, nicotinic acid

Pathophysiology

- insulin resistance → hyperinsulinemia → stimulation of keratinocytes and dermal fibroblast proliferation via interaction with insulin-like growth factor receptor-1 (IGFR1)





# GRANULOMA ANNULARE

Basics

- papular lesions that are often slightly hyperpigmented and depressed centrally
- typically occur on the dorsal surfaces of the hands and feet, and on the extensor aspects of the arms and legs

A number of associations have been proposed to conditions such as diabetes mellitus but there is only weak evidence for this

# SKIN DISORDERS ASSOCIATED WITH MALIGNANCY

Paraneoplastic syndromes associated with internal malignancies:

| Skin disorder | Associated malignancies |
|---|---|
| Acanthosis nigricans | Gastric cancer |
| Acquired ichthyosis | Lymphoma |
| Acquired hypertrichosis lanuginosa | Gastrointestinal and lung cancer |
| Dermatomyositis | Ovarian and lung cancer |
| Erythema gyratum repens | Lung cancer |
| Erythroderma | Lymphoma |
| Migratory thrombophlebitis | Pancreatic cancer |
| Necrolytic migratory erythema | Glucagonoma |
| Pyoderma gangrenosum (bullous and non-bullous forms) | Myeloproliferative disorders |
| Sweet's syndrome | Haematological malignancy e.g. Myelodysplasia - tender, purple plaques |
| Tylosis | Oesophageal cancer |

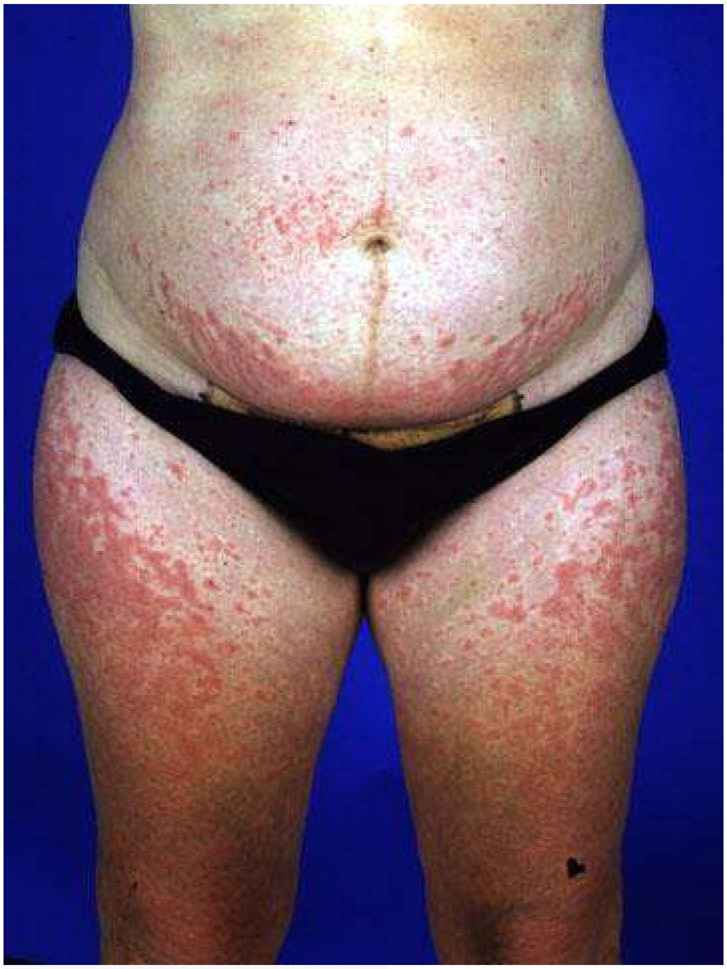
# SKIN DISORDERS ASSOCIATED WITH PREGNANCY

Atopic eruption of pregnancy

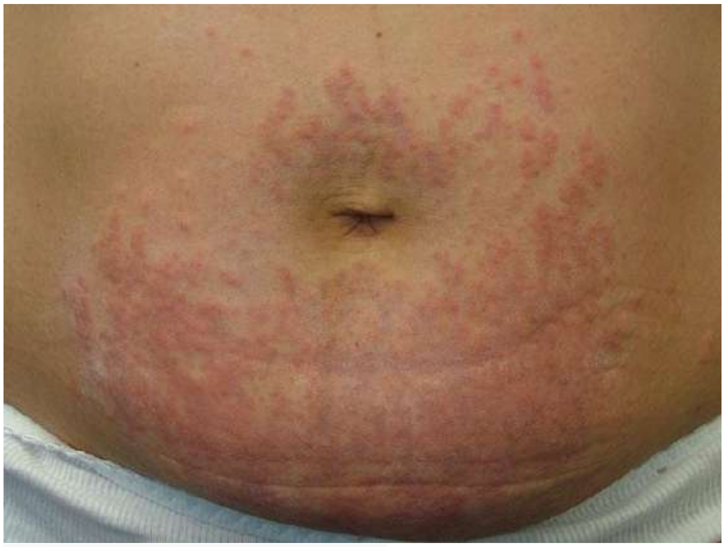
- is the commonest skin disorder found in pregnancy
- it typically presents as an eczematous, itchy red rash.
- no specific treatment is needed

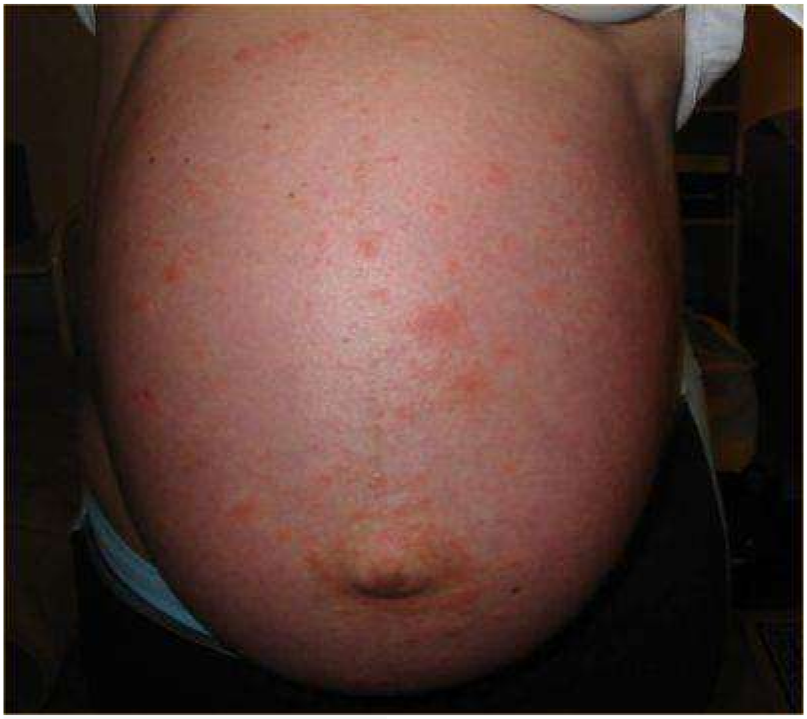
Polymorphic eruption of pregnancy

- pruritic condition associated with last trimester
- lesions often first appear in abdominal striae
- management depends on severity: emollients, mild potency topical steroids and oral steroids may be used



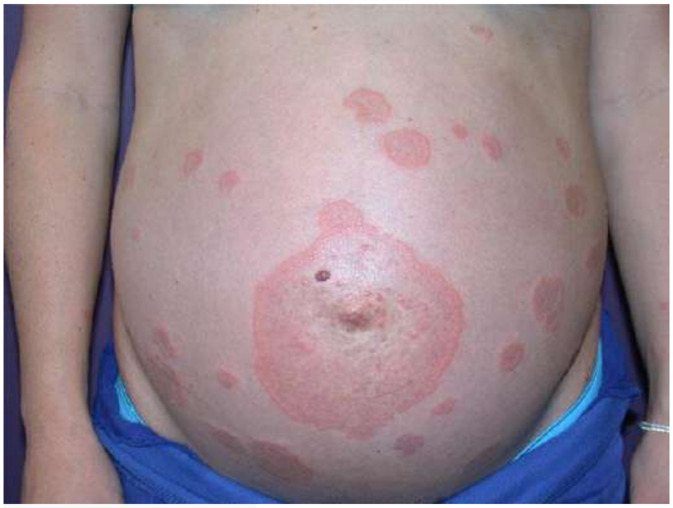
Polymorphic eruption of pregnancy


Polymorphic eruption of pregnancy

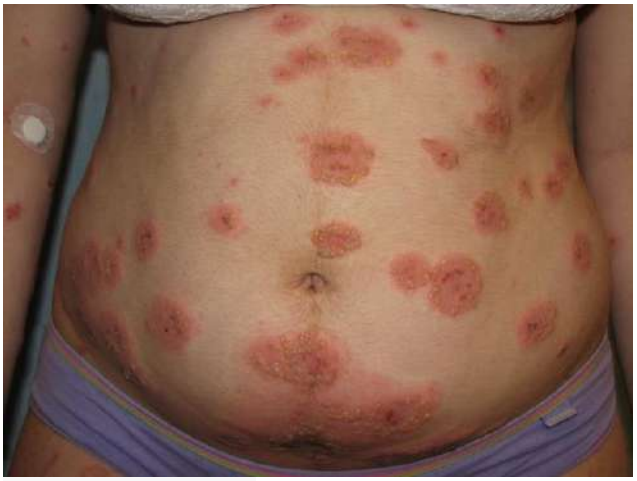

Polymorphic eruption of pregnancy

Pemphigoid gestationis

- pruritic blistering lesions
- often develop in peri-umbilical region, later spreading to the trunk, back, buttocks and arms
- usually presents 2nd or 3rd trimester and is rarely seen in the first pregnancy
- oral corticosteroids are usually required



Pemphigoid gestationis



Pemphigoid gestationis

# SKIN DISORDERS ASSOCIATED WITH TUBERCULOSIS

Possible skin disorders

- lupus vulgaris (accounts for 50% of cases)
- erythema nodosum
- scarring alopecia
- scrofuloderma: breakdown of skin overlying a tuberculous focus
- verrucosa cutis
- gumma

Lupus vulgaris is the most common form of cutaneous TB seen in the Indian subcontinent. It generally occurs on the face and is common around the nose and mouth. The initial lesion is an erythematous flat plaque which gradually becomes elevated and may ulcerate later

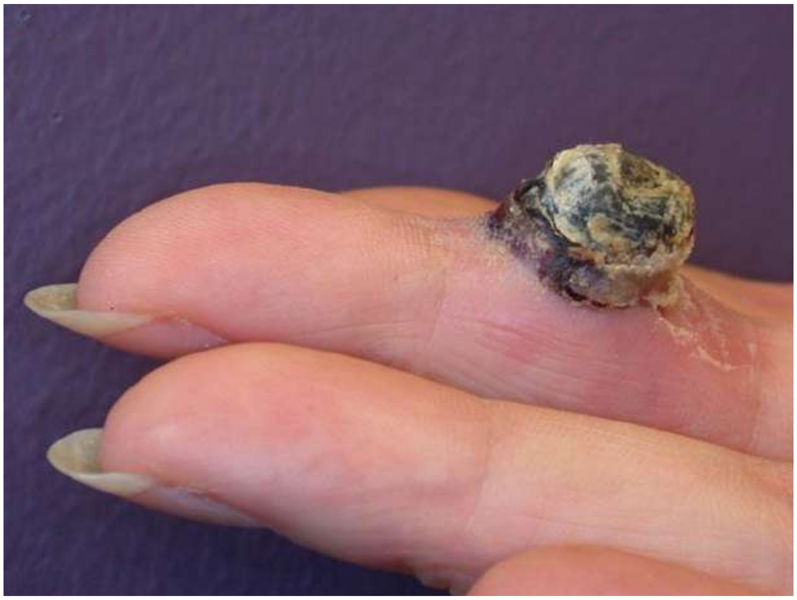
# PYOGENIC GRANULOMA

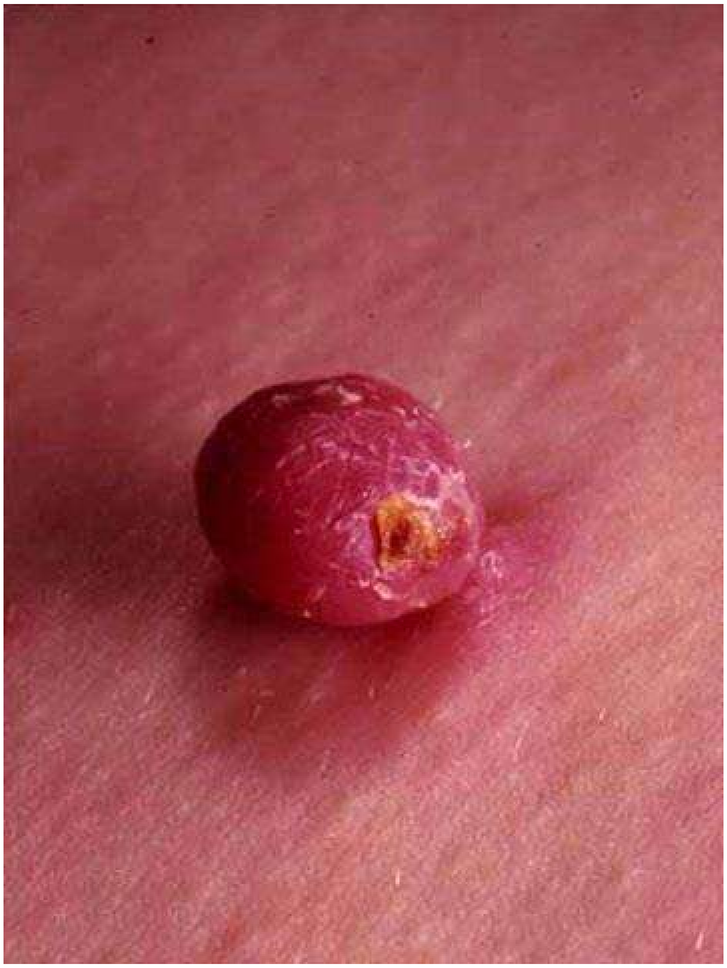
Pyogenic granuloma is a relatively common benign skin lesion. The name is confusing as they are neither true granulomas nor pyogenic in nature. There are multiple alternative names but perhaps 'eruptive haemangioma' is the most useful.

The cause of pyogenic granuloma is not known but a number of factors are linked:
- trauma
- pregnancy
- more common in women and young adults

Features
- most common sites are head/neck, upper trunk and hands. Lesions in the oral mucosa are common in pregnancy
- initially small red/brown spot
- rapidly progress within days to weeks forming raised, red/brown lesions which are often spherical in shape
- the lesions may bleed profusely or ulcerate

Management
- lesions associated with pregnancy often resolve spontaneously post-partum
- other lesions usually persist. Removal methods include curettage and cauterisation, cryotherapy, excision





# SHIN LESIONS

The differential diagnosis of shin lesions includes the following conditions:
- erythema nodosum
- pretibial myxoedema
- pyoderma gangrenosum
- necrobiosis lipoidica diabeticorum

Below are the characteristic features:

Erythema nodosum
- symmetrical, erythematous, tender, nodules which heal without scarring
- most common causes are streptococcal infections, sarcoidosis, inflammatory bowel disease and drugs (penicillins, sulphonamides, oral contraceptive pill)

Pretibial myxoedema
- symmetrical, erythematous lesions seen in Graves' disease
- shiny, orange peel skin

Pyoderma gangrenosum
- initially small red papule
- later deep, red, necrotic ulcers with a violaceous border
- idiopathic in 50%, may also be seen in inflammatory bowel disease, connective tissue disorders and myeloproliferative disorders

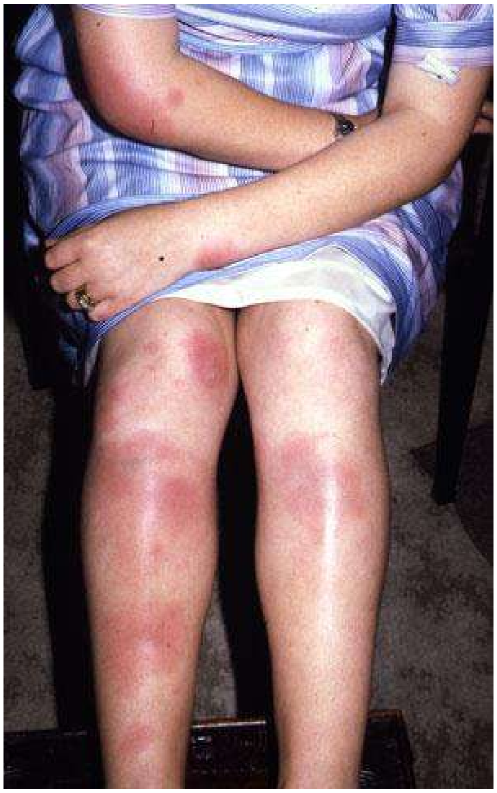
Necrobiosis lipoidica diabeticorum
- shiny, painless areas of yellow/red skin typically on the shin of diabetics
- often associated with telangiectasia

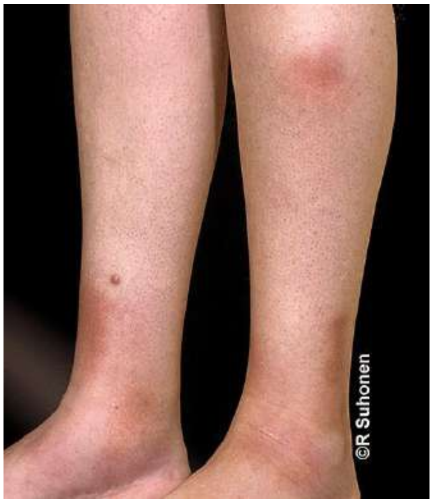
# ERYTHEMA NODOSUM

Overview
- inflammation of subcutaneous fat
- typically causes tender, erythematous, nodular lesions
- usually occurs over shins, may also occur elsewhere (e.g. forearms, thighs)
- usually resolves within 6 weeks
- lesions heal without scarring

Causes
- infection
- streptococci
- tuberculosis
- brucellosis

- systemic disease
- sarcoidosis
- inflammatory bowel disease
- Behcet's
- malignancy/lymphoma
- drugs
- penicillins
- sulphonamides
- combined oral contraceptive pill
- pregnancy





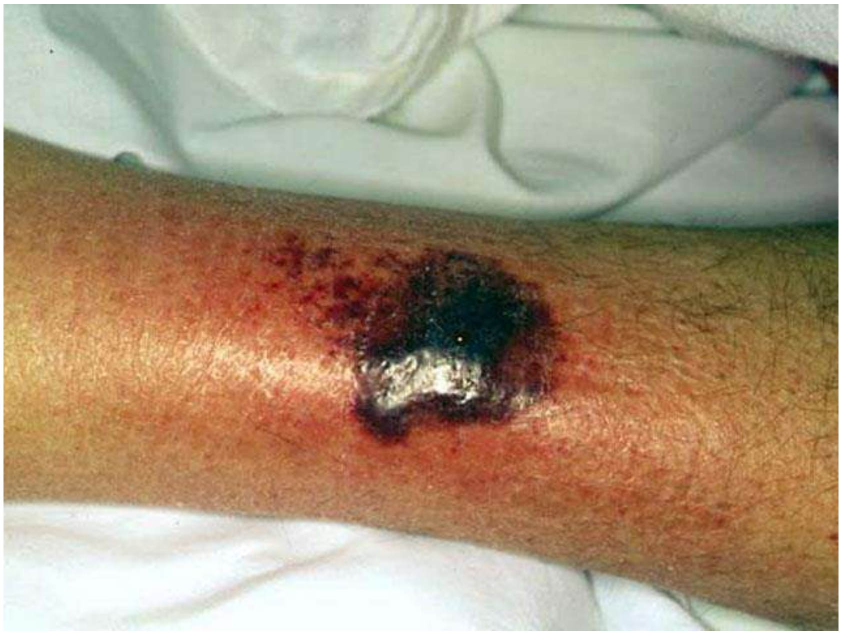
# PYODERMA GANGRENOSUM

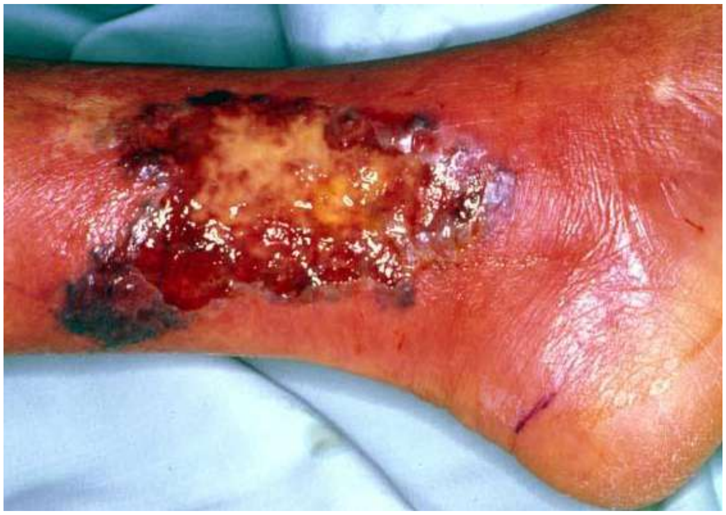
Features
- typically on the lower limbs
- initially small red papule
- later deep, red, necrotic ulcers with a violaceous border
- may be accompanied systemic symptoms e.g. Fever, myalgia

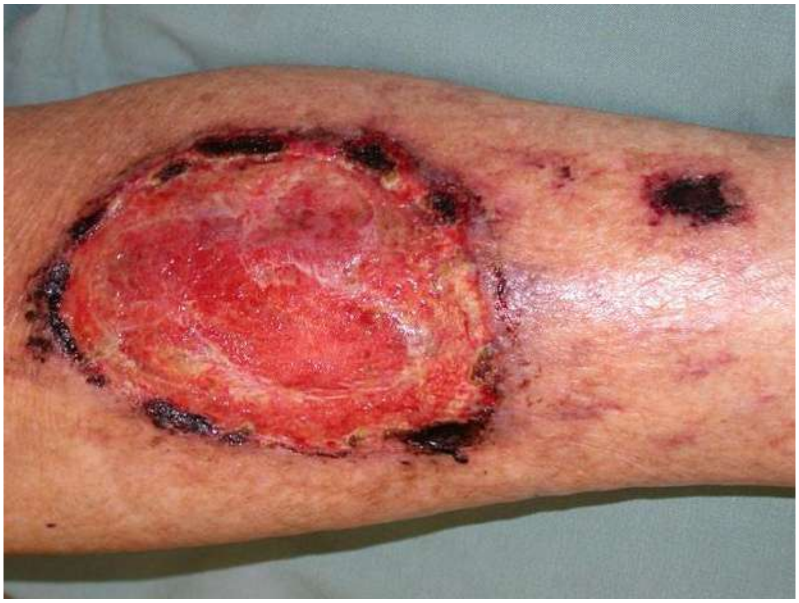
Causes*
- idiopathic in 50%
- inflammatory bowel disease: ulcerative colitis, Crohn's
- rheumatoid arthritis, SLE
- myeloproliferative disorders
- lymphoma, myeloid leukaemias
- monoclonal gammopathy (IgA)
- primary biliary cirrhosis

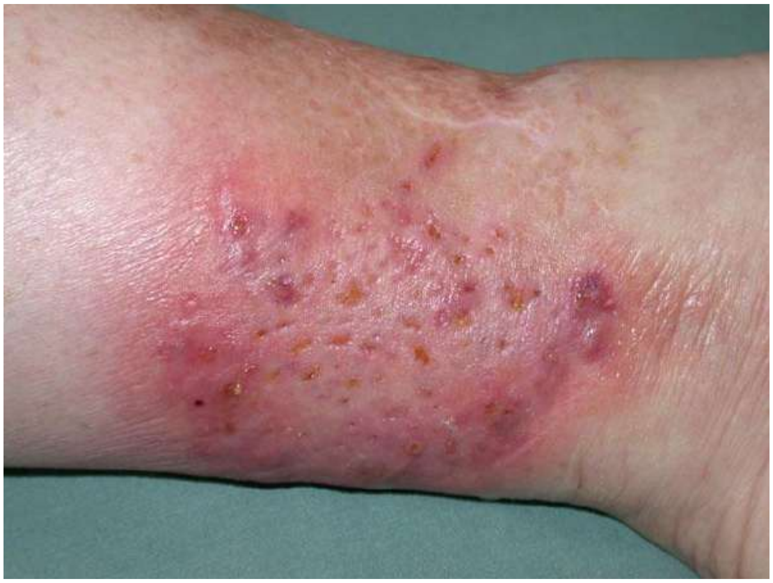
Management
- the potential for rapid progression is high in most patients and most doctors advocate oral steroids as first-line treatment
- other immunosuppressive therapy, for example ciclosporin and infliximab, have a role in difficult cases

*note whilst pyoderma gangrenosum can occur in diabetes mellitus it is rare and is generally not included in a differential of potential causes







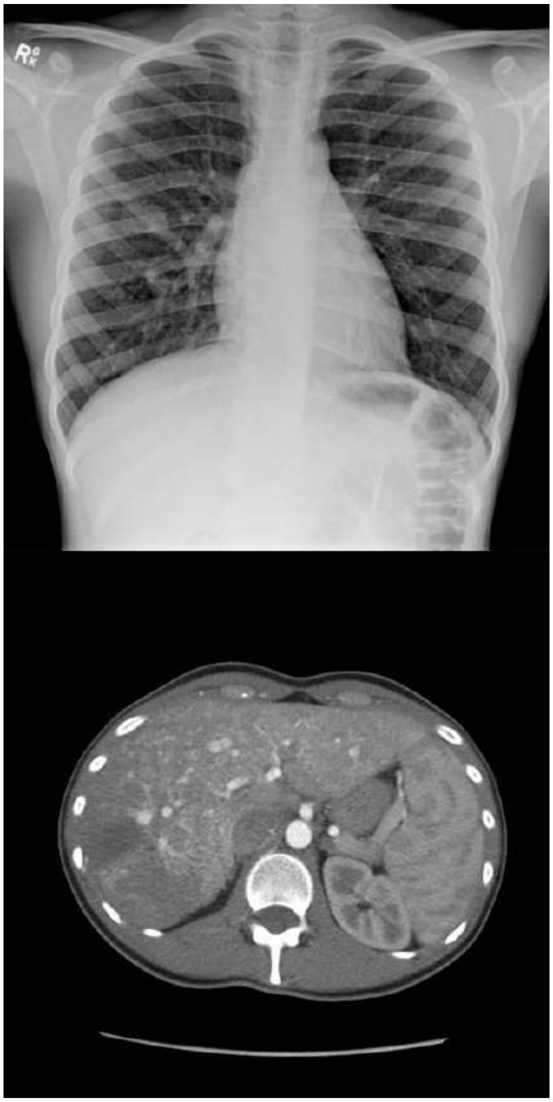


# HEREDITARY HAEMORRHAGIC TELANGIECTASIA

Also known as Osler-Weber-Rendu syndrome, hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant condition characterised by (as the name suggests) multiple telangiectasia over the skin and mucous membranes. Twenty percent of cases occur spontaneously without prior family history.

There are 4 main diagnostic criteria. If the patient has 2 then they are said to have a possible diagnosis of HHT. If they meet 3 or more of the criteria they are said to have a definite diagnosis of HHT:

- epistaxis : spontaneous, recurrent nosebleeds
- telangiectases: multiple at characteristic sites (lips, oral cavity, fingers, nose)
- visceral lesions: for example gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformations (AVM), hepatic AVM, cerebral AVM, spinal AVM
- family history: a first-degree relative with HHT



The chest x-ray shows multiple pulmonary nodules representing arteriovenous malformations, the largest in the right mid-zone. The CT scan shows multiple hepatic arteriovenous malformations

# VENOUS ULCERATION

Venous ulceration is typically seen above the medial malleolus

Investigations

- ankle-brachial pressure index (ABPI) is important in non-healing ulcers to assess for poor arterial flow which could impair healing
- a 'normal' ABPI may be regarded as between 0.9 - 1.2. Values below 0.9 indicate arterial disease. Interestingly, values above 1.3 may also indicate arterial disease, in the form of false-negative results secondary to arterial calcification (e.g. In diabetics)

Management

- compression bandaging, usually four layer (only treatment shown to be of real benefit)
- oral pentoxifylline, a peripheral vasodilator, improves healing rate
- small evidence base supporting use of flavinoids
- little evidence to suggest benefit from hydrocolloid dressings, topical growth factors, ultrasound therapy and intermittent pneumatic compression

# SYSTEMIC MASTOCYTOSIS

Systemic mastocytosis results from a neoplastic proliferation of mast cells

Features
- urticaria pigmentosa - produces a wheal on rubbing (Darier's sign)
- flushing
- abdominal pain
- monocytosis on the blood film

Diagnosis
- raised serum tryptase levels
- urinary histamine

# PELLAGRA

Pellagra is a caused by nicotinic acid (niacin) deficiency. The classical features are the 3 D's - dermatitis, diarrhoea and dementia.

Pellagra may occur as a consequence of isoniazid therapy (isoniazid inhibits the conversion of tryptophan to niacin) and it is more common in alcoholics.

Features
- dermatitis (brown scaly rash on sun-exposed sites - termed Casal's necklace if around neck)
- diarrhoea
- dementia, depression
- death if not treated

# ZINC DEFICIENCY

Features
- perioral dermatitis: red, crusted lesions
- acrodermatitis
- alopecia
- short stature
- hypogonadism
- hepatosplenomegaly
- geophagia (ingesting clay/soil)
- cognitive impairment

# STEVENS-JOHNSON SYNDROME

Stevens-Johnson syndrome is a severe systemic reaction affecting the skin and mucosa that is almost always caused by a drug reaction.

Previously it was thought that Stevens-Johnson syndrome (SJS) was a severe form of erythema multiforme. They are now however considered as separate entities.

Features
- rash is typically maculopapular with target lesions being characteristic. May develop into vesicles or bullae
- mucosal involvement
- systemic symptoms: fever, arthralgia

Causes
- penicillin
- sulphonamides
- lamotrigine, carbamazepine, phenytoin
- allopurinol
- NSAIDs
- oral contraceptive pill

Management
- hospital admission is required for supportive treatment

# TOXIC EPIDERMAL NECROLYSIS

Toxic epidermal necrolysis (TEN) is a potentially life-threatening skin disorder that is most commonly seen secondary to a drug reaction. In this condition the skin develops a scalded appearance over an extensive area. Some authors consider TEN to be the severe end of a spectrum of skin disorders which includes erythema multiforme and Stevens-Johnson syndrome

Features
- systemically unwell e.g. pyrexia, tachycardic
- positive Nikolsky's sign: the epidermis separates with mild lateral pressure

Drugs known to induce TEN
- phenytoin
- sulphonamides
- allopurinol
- penicillins
- carbamazepine

- NSAIDs

Management
- stop precipitating factor
- supportive care, often in intensive care unit
- intravenous immunoglobulin has been shown to be effective and is now commonly used first-line
- other treatment options include: immunosuppressive agents (ciclosporin and cyclophosphamide), plasmapheresis

# ANTIHISTAMINES

Antihistamines (H1 inhibitors) are of value in the treatment of allergic rhinitis and urticaria.

Examples of sedating antihistamines
- chlorpheniramine

As well as being sedating these antihistamines have some antimuscarinic properties (e.g. urinary retention, dry mouth).

Examples of non-sedating antihistamines
- loratidine
- cetirizine

Of the non-sedating antihistamines there is some evidence that cetirizine may cause more drowsiness than other drugs in the class.